*Dissertation on*

# "A CASE CONTROL STUDY TO EVALUATE THYROID DYSFUNCTION AS A RISK FACTOR FOR RETINOPATHY IN TYPE 2 DIABETES MELLITUS"

*Submitted in partial fulfillment of requirements of*

**M. S. DEGREE**

**BRANCH – III (OPHTHALMOLOGY)**

**GOVT. RAJAJI HOSPITAL** &

**MADURAI MEDICAL COLLEGE**

**MADURAI**


**The Tamilnadu Dr. M. G. R. Medical University**

**CHENNAI, TAMIL NADU**

**APRIL 2015**

**Madurai, 24-09-2014**

## BONAFIDE CERTIFICATE

This is to certify that this dissertation titled, **"A CASE CONTROL STUDY TO EVALUATE THYROID DYSFUNCTION AS A RISK FACTOR FOR RETINOPATHY IN TYPE 2 DIABETES MELLITUS"** is a bonafide record of research work done by **Dr. AMIT . K. JAIN,** Post Graduate resident in the Department of Ophthalmology, Madurai Medical College, Madurai.

He has submitted this in partial fulfillment of the regulations laid down by "The Tamil Nadu Dr. M. G. R. Medical University" for award of Master of Surgery Degree, Branch III (Ophthalmology), under our guidance and supervision, during the academic years 2012 - 2015.

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## CERTIFICATE FROM THE GUIDE

This is to certify that this dissertation titled, **"A CASE CONTROL STUDY TO EVALUATE THYROID DYSFUNCTION AS A RISK FACTOR FOR RETINOPATHY IN TYPE 2 DIABETES MELLITUS"** is a bonafide record of research work done by **Dr. AMIT . K. JAIN,** Post Graduate resident in the Department of Ophthalmology, Madurai Medical College, Madurai.

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## DECLARATION

I, **Dr. AMIT. K. JAIN** solemnly declare that, this dissertation entitled "A CASE CONTROL STUDY TO EVALUATE THYROID DYSFUNCTION AS A RISK FACTOR FOR RETINOPATHY IN TYPE 2 DIABETES MELLITUS" has been done by me. I also declare that this bonafide work/a part of this work was not submitted by me/anyone else for any award, for Degree/Diploma to any other University/board either in India/abroad. This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of Master of Surgery degree Branch -III (Ophthalmology) to be held in April 2015.

Dr. AMIT . K. JAIN.

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The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held on 05.03.2014, Wednesday at 10.00 am to 12.00.noon at the Auditorium, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

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The following Projects was approved by the committee.

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|---|---|---|---|
| Dr. Amit K Jain, Amit3987mbbs@gmail.com | PG in M.S., (Ophthalmology) Madurai Medical College and Government Rajaji Hospital, Madurai. | A Case control study to evaluate thyroid dysfunction as a risk factor for retinopathy in type 2 diabetes mellitus. | Approved |

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**To**
**The above Applicant**
**-thro. Head of the Department concerned**

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# PART ONE

# INTRODUCTION

Diabetes Mellitus is the most common endocrine disorder world over and India is considered the world capital of this disease. Among the different types of diabetes Type 2 DM is the most common type. It has a prevalence of nearly 5.5% worldwide and according to WHO statistics there are nearly 147 million people worldwide with Diabetes at present. By 2030 Diabetes would be the 7$^{th}$ leading cause of death and 80% of these deaths would occur in developing and under developed countries.

Type 2 DM affects nearly every physiological process in the body hence its wide ranging systemic effects.

Diabetes, of any variety, is characterized by hyperglycemia, a lack of insulin (absolute or relative), and the development of diabetes-specific micro vascular pathology such as retinopathy, nephropathy and neuropathy. Accelerated atherosclerotic macro vascular disease that affect the blood vessels which supply the heart, brain, and lower extremities is also associated with diabetes.

Diabetic Retinopathy is an important micro vascular complication and is the most common cause of blindness in the developed world. The disease is characterized by progressive changes in retinal microvasculature leading to retinal hypo perfusion, increased

vascular permeability and neovascularization causing severe and permanent blindness.

Thyroid disorders are another common endocrine problems second only to diabetes. Most of the cells in our body need the thyroid hormone for functioning properly as it has effects on a significant number of physiological processes. Hence it is not unusual for an patient to be affected by both Type 2 DM and thyroid disorders. There are varying reports regarding the prevalence of thyroid dysfunction among diabetics, most common thyroid abnormality being sub clinical hypothyroidism.

The two conditions have strong association and have important clinical implications for treatment and insulin sensitivity.

Impaired renal clearance is said to be an important cause of the reduction in insulin requirements in hypothyroidism. Decreased gluconeogenesis makes these patients highly prone for hypoglycemia.

Diabetic patients have a increased frequency of retinopathy and nephropathy when associated with subclinical hypothyroidism. At the same time the severity of retinopathy in these patients is said to be more. Even subclinical hypothyroidism has a negative impact on lipid metabolism and it is an independent risk factor for myocardial infarction and retinopathy.

Another possible mechanism linking Subclinical hypothyroidism to vascular diseases is the finding that thyroid hormones inhibit collagen induced platelet aggregation and directly relax smooth muscles.

Further hypothyroidism is accompanied by a hypercoagulable state and increased blood viscosity.

Hyperthyroidism is seen less commonly in Diabetes, but is associated with higher risk of development of potentially life-threatening ketoacidosis. Therefore, detection and correction of thyroid abnormalities is essential for proper diabetic control as well as for prevention of diabetic complications as it may greatly increase the quality of life in these patients.

At the molecular level**, thyroid hormone has cell surface receptors for integrin αvβ3 that mediates the angiogenetic activity of thyroid hormones and integrin αvβ3 has pro - angiogenic effects on growth factors implicated in the pathogenesis of retinal new vessels,** including erythropoietin, growth hormone, basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), and VEGF.

Thyroid hormone has well documented effects on new vessel formation. These effects are mediated via integrin receptor for the thyroid hormones on the vascular smooth muscle cells and endothelial cells and reflect the relation between genomic and nongenomic mechanisms invoked by the thyroid hormones.

## REVIEW OF LITERATURE

### DIABETES MELLITUS AND THYROID

The term ‘diabetes’ has been derived from Greek word ‘dia’ (through) and ‘bianeon’ (to go), meaning a siphon, “because fluid does not remain in body but uses man’s body as a ladder whereby to leave it as if patient was a siphon” which described polyuria, by the legendry Greek physician Aretaeus . He described the disease as “… melting down of flesh into urine, thirst unquenchable, kidneys never stop making water”

During $5^{th}$ and $6^{th}$ century BC, sweet taste of urine in polyuric patients was also described in Sanskrit (Indian) literature by Susruta, Charaka and Vaghbata and the disease was named “Madhumeha”. They described that the urine of these patients tasted like honey (madhu), sticky to touch and ants were strongly attracted to it. They differentiated two forms of the disease, one affecting thin people who do not survive long and the other, affecting older and obese. They also described relation of diabetes to hereditary, obesity, sedentary life and diet. This description was parallel to the subdivision of diabetes into type 1 and 2 diabetes.

Indian literature gets credit for the term “honey urine” referring to the clear colourless nature of diabetic urine.

## THE THYROID GLAND

The thyroid gland was known at least from the time of Galen, who thought it provided a fluid for the lubrication of the larynx.

Andrecos Vesslius (1514-64) gave the first description of the thyroid gland as two glands on each side of the root of the larynx which are large fungus like, flesh colored and covered with blood vessels.

Eustachius (1520-74 Ad) discovered the isthmus of the thyroid gland. The anatomical site, size and weight were described by Wharton (1614-73 AD) in his book Adenographia.

Scharge noted special blood supply of the thyroid. It was alberchut Von hallen (1768 - 78) who classified thyroid among the ductless gland.

The Thyroid hormone, thyroxine was first isolated by Dendall of Mayo clinic in 1915. CR. Harrington (1925) determined the chemical constitution and devised means for artificial synthesis and pointed out the principal chemical features responsible for specific physiological activity (F Cuelly 1961).

Endemic goitre was known to doctors of antiquity in India, china and Greece.

## CRITERIA OF AMERICAN DIABETIC ASSOCIATION FOR DIABETES MELLITUS DIAGNOSIS

1. A1C ≥ 6.5%. This test must be performed in a lab using a technique that is certified by the NGSP and standardized to the Diabetic control and complication trial(DCCT)assay.*

OR

2. FPG > 126 mg/dl (7.0mmol/l). Fasting is defined as plasma glucose after 8 hours fasting (no calorie intake).

OR

3. 2-h plasma glucose load of ≧ 200 mg/ dl (11.1 mmol/ l) during an OGTT. The test should be done as described by the WHO, after giving a glucose load that is the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with symptoms of hyperglycaemic crisis or hyperglycaemia, a random glucose of ≧ 200 mg/dl(11.1 mmol/l)

*In the absence of unequivocal hyperglycemias, criteria 1-3 should be confined by repeat testing.

DIABETES MELLITUS – CHRONIC COMPLICATIONS

**Microvascular complications**

Eye disease

Nephropathy

Retinopathy (nonproliferative/proliferative)

Macular edema

Neuropathy (Motor , sensory and autonomic)

(mono - and polyneuropathy)

**Macrovascular complications**

Cerebrovascular disease

Coronary artery disease

Peripheral vascular disease

**Others**

Genitourinary (sexual/ uropathy dysfunction)

Dermatologic

Gastrointestinal (gastroparesis, diarrhea)

Increased risk of infections

Cataracts

Glaucoma

Dental abnormalities

## RETINAL ANATOMY AND PHYSIOLOGY

The retina ("network") consists of five fundamental types of cellular elements: neurons, glial cells, microglia, blood vessels, and pigment epithelium. Intact connections and communications between these cells are required for normal vision.

*Neurons*- The neurons and glial cells of the retina comprise more than 95% of the retinal mass, but they are transparent to visible light, so their structure and function are not readily apparent on clinical examination.

Primarily the retina is a neural tissue, and retinal neurons, the cells that define vision, include photoreceptors, amacrine, bipolar, horizontal, and ganglion cells. Electrical inputs from the first four types of neurons converge on the ganglia, and the ganglion cells' electrical output is conducted to the brain via axons of the nerve fiber layer and optic nerve. The high degree of convergence and integration of retinal signals is evident in the 10:1 ratio of photoreceptors (≈130 million) to ganglion cells (≈1.2 million) per human eye. Therefore, disruption of any of the neuronal layers interferes with vision, but redundancy of the neuronal architecture allows for many cells to die or malfunction before visual function is impaired. For example, at least 50% of ganglion cells in an area are lost before a clinically detectable visual defect is apparent in

patients with glaucoma, and an eye can retain 20/20 acuity with less than 10% of cone photoreceptors.

*Glial Cells*- The glial ("glue") cells of the retina— astrocytes and Muller cells —act as supporting cells for the blood vessels and neurons. They regulate extracellular ion concentrations necessary for generating action potentials, metabolize neurotransmitters such as glutamate, and transport substrates for retinal metabolism (glucose, lipids, and amino acids) from blood vessels to neurons. Their role in glutamate handling is particularly important because excess glutamate in response to retinal ischemia or diabetes is toxic to neurons and may contribute to neuronal cell death.

In addition to their effects on neurons, astrocytes guide fetal vascular development from the optic nerve to the peripheral retina and influence the function and integrity of mature vessels. Major cytokine involved in this process is vascular endothelial growth factor and is produced by astrocytes and Muller cells. Astrocytes also signal blood vessels to acquire barrier properties to form the blood–retina barrier and influence the development of tight junctions in retinal endothelial cells , and regulate the function of retinal synapses and, therefore, visual function. However, many details of the means by which glial cells control normal retinal function remain uncertain.

*Microglial Cells*- Microglia are bone marrow-derived macrophages that reside in the retina and sense the retinal metabolic environment. They respond to a variety of stimuli, such as retinal detachment, infection or trauma (including laser photocoagulation) by proliferating, migrating, and releasing inflammatory cytokines, such as interleukin-1, VEGF, and tumor necrosis factor-α. Retinal injury increases the migration of bone marrow-derived immune cells into the retina and their differentiation into microglia cells. In the short term, these responses may represent a beneficial response to the injury, but prolonged activation results in chronic inflammation and cellular damage.

*Blood Vessels*- The retinal vascular circuit consists of conduits into and out of the retina. Precapillary arterioles, capillaries, and postcapillary venules are included in microcirculation. Smooth muscle cells in arterioles allow the arterioles to change their radius and dynamically regulate local delivery of blood to the retina. Precapillary arterioles are the primary resistance vessels, whereas venules have a high density of receptors for vasoactive agents, such as histamine. Passive conducting tubes are primarily the venules, which drain blood out of the retina. Capillaries and venules are the primary sites of fluid diffusion into the retina under normal conditions, and this diffusion increases in pathologic conditions such as diabetes.

Blood vessels of the central nervous system have a general feature of autoregulation by which the organ maintains appropriate blood flow despite changes in systemic arterial pressure. Smooth muscle cells in retinal arterial vessesls, while pericytes in capillaries, arterioles, and venules, function as modified smooth muscle cells. These features allow the retinal circulation to autoregulate in response to local and systemic metabolic demands. Blood vessels also autoregulate in response to the partial pressure of the oxygen (pO2) and carbon dioxide (pCO2). Therefore, vessels constrict in response to hyperoxemia and dilate in response to hypercapnea. Under normal conditions, retinal blood flow balances nutrient delivery and waste removal with retinal metabolism. Diabetes, a systemic malfunction of carbohydrate,lipid, and protein metabolism, leads to vascular and tissue damage in organs such as the retina. Thus, diabetic retinopathy is fundamentally a disorder of retinal and systemic metabolism that damages the retinal tissue elements and associated vessels; that is, a neurovascular degeneration or sensory neuropathy.

| **Clinical Risk Factors for Diabetic Macular Edema and Retinopathy** |
| --- |
| Poor metabolic control |
| Hypertension (>130/80 mm Hg) |
| Intravascular fluid overload |
| Congestive heart failure |
| Renal failure |
| Hypoalbuminemia |
| Anemia—Erythropoietin effects on retina |
| Hyperlipidemia |

## PRECLINICAL RETINOPATHY

In patients with Type 2 diabetes, it is more difficult to determine the interval between the development of diabetes and the development of retinopathy because it is believed that 4 to 7 years generally elapse between the onset of non-insulin dependent diabetes and its diagnosis.

There is now ample evidence that functional and anatomic changes occur before the onset of vascular lesions in both types of diabetes. In the International Diabetic Retinopathy classification this phase corresponds to stage ‘0’. Diabetic patients without retinopathy generally do not have any specific visual symptoms. Nevertheless, subtle defects in neurosensory retinal function have been demonstrated by sensitive testing methods, including decreased blue -yellow color perception and contrast sensitivity. In addition, the oscillatory amplitudes on the b-wave of electroretinogram (ERG) may be reduced. Mulifocal ERG and short-wavelength, and white-on-white perimetry testing reveal regional depression of retinal function in diabetic patients before the onset of vascular lesions .These tests indicate dysfunction of the inner retina, especially bipolar, amacrine, and ganglion cell neurons. Nerve fiber layer defects may also be detected by red free photography or scanning laser ophthalmoscopy in diabetic patients with minimal or no vascular lesions. Together, these findings provide strong evidence that

retinal function may be altered prior to the onset of vascular lesions and that diabetic retinopathy is not strictly a vascular disease.

Experimental studies have demonstrated increased neural cell injury within 1 month of diabetes, long before the onset of typical vascular lesions. This accelerated cell death results in loss of the inner plexiform layers and ganglion cell, with retinal thinning. Recently studies have revealed loss of cholingergic and dopaminergic amacrine cells, remodeling of dendrites, and reduction of essential proteins of synapses as early neurodegenerative changes in diabetic retinopathy. Together, these subtle cellular changes may contribute to reduced oscillatory potentials in the ERG. Optic nerve axon size also decreases as part of the degenerative response of neural tissue to the metabolic stress of diabetes. The cause of these degenerative processes is highly complex but may include loss of neurotrophins (insulin, brain-derived neurotrophic factor), excess nutrients (glucose, amino acids, and lipids), inflammation, and excitotoxicity. Muller cells and astrocytes control glutamate metabolism, so glutamate accumulation in the extracellular fluid between neurons and glia implies that glial cells are defective, and the clearance of retinal glutatmate is impaired in experimental diabetes. Glutamate is a well-recognized cause of neuronal cell death in cerebral ischemia (glutamate excitotoxicity).

Vascular changes that begin shortly after the onset of insulin-deficient diabetes include delayed white blood cell migration in perifoveal capillaries , increased blood–retina barrier permeability , and increased retinal blood flow compare to non-diabetic control subjects .These findings suggest that vascular autoregulation is impaired before clinically evident vascular lesions appear.

Thus, while this early phase of diabetic retinopathy appears to be innocuous from a clinical standpoint, numerous cellular and metabolic processes are active that lead to the development of clinically evident nonproliferative diabetic retinopathy (NPDR). Indeed, a recent demonstration that retinal flavoprotein fluorescence increases in diabetic patients before the onset of visible retinopathy is strong evidence for early onset of metabolic dysregulation.

While it is reassuring that patients with diabetes may have no visible retinopathy, the absence of microaneurysms or hemorrhages should not lead to complacency on the part of patients or physicians. In fact, aggressive control of the metabolic and systemic cardiovascular risk factors known to exacerbate retinopathy onset and progression provides an ideal opportunity to prevent vision-threatening changes.

Patients who have not developed retinopathy should have a treatment strategy designed to optimize the chance to maintain vision. These patients with healthy appearing retinas and good vision represent

the greatest therapeutic opportunity, particularly in light of the emerging diabetes epidemic.

## Preclinical Retinopathy

| Symptoms | Clinical Signs | Abnormal Test Results | Histopathology | Cellular Events |
|---|---|---|---|---|
| Usually none | Normal appearing Retina | Color perception: decreased blue-yellow sensation activation (deuteranomaly)<br><br>ERG: decreased oscillatory potential amplitudes<br><br>Visual field defects<br><br>Vitreous fluorometry: increased blood–retina barrier permeability | Neural cell apoptosis<br>Microglial cell Activation<br><br>Nerve fiber layer loss<br><br>Glial cell dysfunction: increased glutamate | Decreased vascular tight junctions<br><br>Vascular basement membrane thickening |

## NONPROLIFERATIVE DIABETIC RETINOPATHY

NPDR is defined and staged by ophthalmoscopic features such as vascular lesions, including microaneurysms, intraretinal hemorrhages, and vasodilation. The definitions (nonproliferative and proliferative) are useful clinically because they permit evaluation of visible ocular risk factors for moderate and severe visual loss. The specific sequence of cellular events that lead to the features of NPDR remain uncertain because they occur below the resolution Although pericytes and endothelial cells clearly undergo programmed cell death (apoptosis), it is unproven whether pericytes are uniquely susceptible to diabetes. The original light microscopic study of trypsin digest preparations in which the neural retina is removed to reveal the vascular network did not indicate the specific anatomic site from which the photos were taken, gave no statistical analysis of pericyte dropout or other morphologic lesions, and did not determine whether pericyte loss occurred in areas without microaneurysms. Another study questioned whether pericytes are lost first or preferentially in diabetic retinopathy.

Therefore, while pericytes undoubtedly change in diabetic retinopathy, they do not appear to be the earliest cellular defects, and the specific functional consequences are still unclear. Cotton-wool spots have been considered to represent focal infarcts of the nerve fiber layer due to local microvascular occlusion. However, cotton wool spots have also

been described in diabetic persons without clinical or fluorescein angiographic evidence of vascular occlusion and may resolve without detectable nerve fiber layer loss. Hence, it is likely that the loss of axonal transparency that appears as retinal whitening results from impaired axonal metabolism and axonal transport, particularly in patients with poorly controlled diabetes.

Some young patients (<45 years old) exhibit focal depressions in the macular reflex, the "**retinal depression sign**". This sign results from small retinal depressions that reflect light away from the observer so that the macula appears slightly darker than the surrounding retina. The feature is best observed by slit-lamp biomicroscopy and is also noted on fundus photographs, particularly with red-free filters. It is more easily recognized in young patients who have a bright foveal reflex than in older persons. The thinning may result from macular ischemia and/or nonischemic neuroretinal degeneration (apoptosis). This finding may contribute to paracentral scotomas and may be confused with epiretinal membranes or macular edema.

The cellular and biochemical events that results in vascular lesions in diabetic retinopathy are uncertain in humans and complex. While it is clear that intensive treatment of diabetes in humans or animals significantly delays the progression and onset of retinopathy, it is not known whether the retinopathy development represents a direct result of

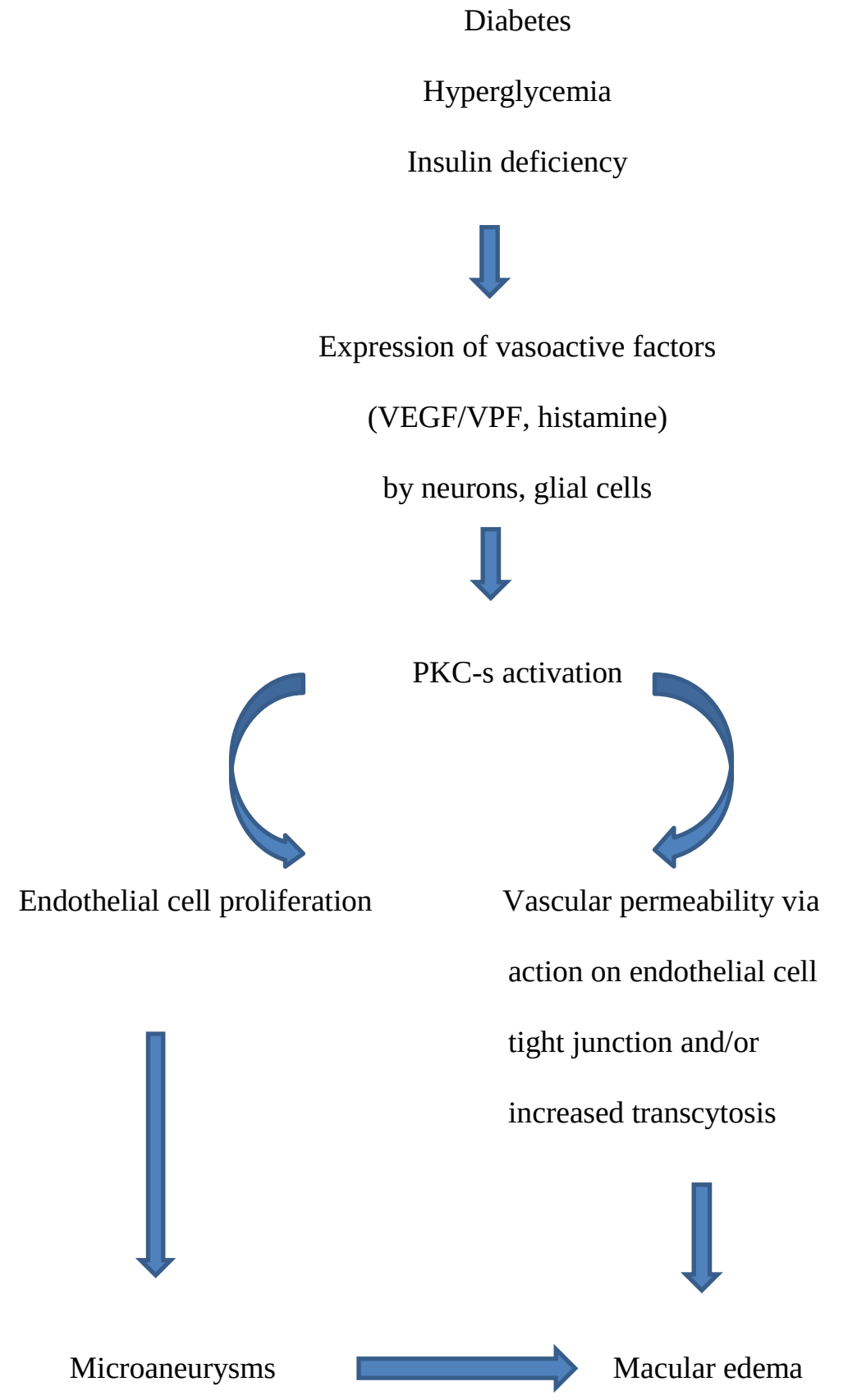
insulin resistance or insulin deficiency, a consequence of hyperglycemia, or another metabolic derangement associated with diabetes, such as increased lipids. The metabolic pathways that have an association with diabetic retinopathy include activation of the polyol pathway, nonenzymatic glycosylation, and activation of the s isoform of protein kinase C (PKC-s). Increased glucose metabolism via the polyol pathway , has also been considered to account for diabetic retinopathy and peripheral neuropathy. The hypothesis suggests that increased glucose metabolism via this pathway results in the accumulation of sorbitol, reduction of myo - inositol, and/or reduction in activity of sodium-potassium-ATPase, which may account for vascular dysfunction. Aldose reductase is a key enzyme in the polyol pathway. However, specific vascular functional or neuronal abnormalities, such as barrier breakdown or capillary closure, have not been fully explained by this hypothesis.

Another theory for the development of diabetic retinopathy involves vascular damage by advanced glycosylation end products (AGEs). According to the concept of nonenzymatic glycosylation , sugar molecules bond covalently to reactive molecules and cause alterations in the functions of proteins, nucleic acids, and cells, such as macrophages. This reaction gives rise to the glycohemoglobin (hemoglobin $A1_c$) test, which measures integrated glucose levels over 3 months. Cross-linking of long-lived proteins such as collagens has been proposed to due to

nonenzymatic glycosylation, which are found in vitreous and vascular basement membranes. Collagen cross-linking may decrease the turnover of collagen and may contribute to vitreous collagen contraction and allow for basement membrane thickening . Advanced glycation end products increase in Muller cells in experimental diabetes, and a AGE receptor(soluble) that blocks its activation, decreases cell death of neurons.

Thus, in spite of a likely role, there is no experimental evidence that demonstrates that excess glucose alone is necessary or sufficient to cause retinopathy or other complications in diabetes. Another metabolic mechanism involves a specific molecule in signal transduction cascades. Protein kinase C adds phosphate groups to serine or threonine residues of cytoplasmic proteins. This enzyme also phosphorylates other proteins in the signal transduction cascade of VEGF and histamine, and is associated with alterations in retinal blood flow and blood–retina barrier breakdown. An oral agent that inhibits PKC-s activity (ruboxistaurin, Eli Lilly Co) reduced the risk of visual loss in persons with diabetic macular edema and visual acuity , however it did not bring about any change in the risk of developing neovascularization in diabetic patients with severe non proliferative diabetic retinopathy. VEGF production by nonvascular retinal cells, including astrocytes, Muller cells, and ganglion cells, indicating that increased vascular permeability may be the consequence

of vasoactive compounds originating in the neural retina acting secondarily on the microvasculature. This observation is further evidence that diabetic retinopathy may not be a primary vascular disease.




**Possible mechanism for development of nonproliferative diabetic retinopathy.**

## Nonproliferative Diabetic Retinopathy

| Symptoms | Clinical Signs | Abnormal Test Results | Histopathology | Cellular Events |
|---|---|---|---|---|
| None, Blurred Vision, or Glare | Retinal vasodilation<br>Microaneurys-m<br>Cotton-wool spots<br><br>Intraretinal Hemorrhages<br><br>IRMAs, Venous beading<br>Retinal depression Sign | Intravenous fluorescein angiography: vascular leakage and occlusion<br>ERG: depressed oscillatory amplitudes<br><br>Increased retinal blood flow<br><br>Visual field Defects | Microaneurysms, intraretinal hemorrhages in nerve fiber layer and outer plexiform layer<br><br>Cytoid bodies, nerve fiber layer swelling<br><br>Neuronal loss and degeneration, lipid exudates and extracellular edema in outer plexiform layer; nerve fiber layer atrophy<br>Glial cell occlusion of capillaries | Increased VEGF expression by neurons and glial cells<br><br>Vascular cell Apoptosis<br><br>Glial cell activation and macrophage infiltration |

## DIABETIC MACULAR EDEMA

The physiologic factors that govern the development of DME are similar to those involved in tissue edema elsewhere in the body, and understanding the pathophysiology of DME allows construction of a set of risk factors and treatment principles for DME.

Starling's law of the capillary states that edema formation in tissues from fluid flux across the capillary wall is related to the hydrostatic pressure gradient (blood pressure minus tissue pressure) less the oncotic pressure that draws water into the vessels. This relationship has recently been shown to also operate in the retina for DME. That is, increased intravascular hydrostatic pressure from hypertension or intravascular fluid overload drives fluid across the vascular wall and leads to increased fluid accumulation in the macula. The oncotic force that pulls water from tissue into capillaries is determined by the plasma albumin concentration, so when albumin levels decrease below 3.0 mg/dL, the oncotic pull is sufficiently diminished to contribute to tissue edema. Patients with diabetes frequently have impaired Starling's equilibria. The clinical risk factors for DME include increased intravascular volume due to hypertension, fluid overload (congestive heart failure and renal failure) and hypoalbuminemia from diabetic nephropathy.

Venous tortuosity and dilation are frequently noted in patients with progressive retinopathy. The physiologic basis of this feature owes to autoregulatory vasodilation of arterioles that causes intravascular pressure in the arterioles to decrease and that in the venules to increase, according to Poiseuille's Law. The increased hydrostatic pressure also leads to greater blood vessel length and tortuosity, per LaPlace's Law. Serial observations in patients with diabetes have shown that retinal vascular diameter and length increase prior to the onset of DME and improve following macular photocoagulation for DME and after panretinal photocoagulation for proliferative diabetic retinopathy (PDR).

In addition to altered autoregulation of vascular flow, the intrinsic integrity of the retina-blood barrier is also impaired. Studies with vitreous fluorometry in humans show that breakdown of the inner retina-blood barrier (as a result of tight junctions between vascular endothelial cells) predominates over changes in the outer barrier (tight junctions between retinal pigment epithelial cells) in early DME . The outer barrier breaks down in patients with chronic DME. The proteins that comprise the tight junctions between vascular endothelial cells are reduced in early experimental diabetes, and this may account for increased vascular permeability. As such, the hemodynamic abnormalities in the retina are analogous to those that occur in the kidney in early diabetes; that is,

increased renal blood flow and increased glomerular permeability, with resultant albuminuria.

Other factors may also aggravate the overall severity of retinopathy. For example, hyperlipidemia has been associated with an increased risk of hard exudates and macular edema, and anemia is associated with worsening of retinopathy in general. Anemia may impair oxygen delivery to the retina. In addition, erythropoietin may serve as a trophic factor for retinal cells and its deficiency might aggravate retinal cell death. Conversely, excessive intraocular erythropoietin levels may contribute to the development of DME and PDR.

Together, these risk factors give rise to principles of DME treatment, including improving metabolic control, blood pressure, fluid overload, anemia, and hyperlipidemia.

Microaneurysms are the most characteristic ophthalmoscopic features of diabetic retinopathy. They occur throughout the posterior pole and are often first noted temporal to the macula. Their importance lies in their association with the retinopathy severity and as sources for leakage of fluid and lipid transudates.

Histologically, they are outpouchings of the capillaries, with focal endothelial cell proliferation and pericyte loss, often adjacent to areas of nonperfusion. The factors that contribute to microaneurysm formation likely include structural features (loss of supporting pericytes

and astrocytes), hemodynamic alterations (increased capillary intramural pressure), and local production of vasoproliferative factors, such as VEGF. Like cotton wool spots, retinal thickening, and hemorrhages, microaneurysms can wax and wane through the course of retinopathy.

Understanding the pathophysiology of DME allows construction of a set of systemic risk factors, such as poor glycaemic control, systemic arterial hypertension, increased lipid levels, and low albumin levels.

| **Mechanisms of Diabetic Macular Edema** |
| --- |
| Poor glycaemic control<br>Increased hydrostatic pressure<br>Hypertension<br>Intravascular fluid overload (congestive heart failure, renal failure)<br>Decreased colloid oncotic pressure<br>Low albumin levels<br>High lipid levels<br>Anemia |

## PROLIFERATIVE DIABETIC RETINOPATHY

PDR, characterized by new vessels on the optic nerve head, retina, and/or iris, may be an aberrant attempt to alleviate hypoxia in eyes with severe capillary closure or other retinal ischemia. The new vessels grow perpendicular to the plane of the retina into the scaffolding provided by the vitreous cortex, typically from venules at the junction of perfused and nonperfused retina. In contrast to normal retinal vessels, which are ensheathed by intact astrocytes, neovascularization is associated with reactive glial cells which do not allow endothelial cell tight junctions to form completely, with resultant hyperfl-uorescence noted on fluorescein angiography. PDR, first involves angiogenesis (neovascularization), followed by macrophage infiltration, remodeling of the vessels, with subsequent fibrosis, and eventual replacement of the vascular tissues by collagen.

The natural history of untreated PDR includes fibrosis of the neovascularization, inducing traction on the retina. Subsequent contraction may induce preretinal hemorrhage, vitreous hemorrhage, and traction retinal detachment. Panretinal photocoagulation alters the healing response by reducing the neovascular proliferation, and inducing quiescence.

The cellular events that lead to neovascularization may include retinal hypoxia, elaboration of factors that stimulate endothelial cell

proliferation, macrophages and vitreous contraction. Numerous factors have been implicated in the pathogenesis of retinal new vessels, including erythropoietin, growth hormone, basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), and VEGF. Together, these "growth factors," cytokines, and cells comprise an inflammatory response. As noted above, VEGF is produced by cells in the neurosensory retina and acts by specific endothelial cell surface receptors to induce neovascularization. VEGF levels are increased in the vitreous of eyes with new vessels and subsided after panretinal photocoagulation.

Inhibition of VEGF action by antisense oligonucleotides that inhibit VEGF messenger RNA or by antibodies that bind the protein before it can activate its receptors reduces neovascularization. After panretinal photocoagulation or intravitreal bevacizumab injection, VEGF levels diminish and those of connective tissue growth factor (CTGF) increase, changing the wound healing response from angiogenesis to fibrosis.

VEGF production is not unique to diabetic retinopathy, and is also increased in retinopathy of prematurity and other ocular neovascular processes, as well as in physiologic conditions (menstruation and wound healing) and in pathologic vascularization (tumors) throughout the body. The control of retinal angiogenesis is complex,and the molecular puzzle

is still being unraveled. Vitreous collagen crosslinking via nonenzymatic glycosylation may contribute to vitreous contraction.

Diabetic retinopathy involves both vascular and neural elements of the retina from the early stages of diabetes through the development of PDR. Improved means of preventing visual loss in diabetes depend on a better understanding of the underlying mechanisms and the altered relationships between the neural retina and blood vessels.

Hypoxia of retinal neurons, glial cells

Release of factors that increase vascular permeability

and endothelial cell mitosis (VEGF, probably others)

Proliferation of new vessels through

internal limiting membrane

Growth of new vessels into posterior vitreous cortex

Glial cell proliferation* → epiretinal membranes

Contraction of vitreous and traction on new vessels

Vitreous hemorrhage, traction retinal detachment

**Mechanisms of proliferative diabetic retinopathy**

## Proliferative Diabetic Retinopathy

| Symptoms | Clinical Signs | Abnormal Test Results | Histopathology | Cellular Events |
|---|---|---|---|---|
| None, reduced vision, nyctalopia or floaters | Retinal signs: neovascularization of optic disc, retina and/or iris, retinal vasodilation beading, and IRMAs<br><br>Vitreous signs: vitreous cells, contraction, and opacification of posterior hyaloid face, partial posterior vitreous detachment with epiretinal membranes, and traction retinal detachment | Intravenous fluorescein angiography: severe capillary closure and hyperfl - uorescence of neovascularization with leakage<br><br>Dark daptation: impaired<br>Ultrasonography: partial posterior vitreous detachment with vitreoretinal adhesions; retinal detachment | Glial cell proliferation and epiretinal membranes<br><br>Endothelial cell Proliferation<br><br>Intraretinal Haemorrhage<br><br>Cystoid macular Edema<br><br>Neuronal loss, retinal detachment | Vitreous collagen cross-linking<br><br>Endothelial cell mitosis<br><br>Glial cell Proliferation<br><br>Occluded Capillaries |

## CLASSIFICATION OF RETINOPATHY

Historically, diabetic retinopathy has been classified based on ophthalmoscopic findings, ranked into a stepwise scale from no retinopathy through various stages of non-proliferative or pre-proliferative disease to advanced proliferative disease ranked on a continuous scale from no retinopathy to advanced proliferative diabetic retinopathy(PDR) with Non-Proliferative diabetic retinopathy(NPDR) falling somewhere in the middle of the continuum. However, this grading may not accurately reflect functionally severe disease since maculopathy with severe visual loss may occur in the presence of moderate ophthalmoscopic signs.

There are two different systems of classification for diabetic retinopathy. One is designed for the ophthalmologist and covers all the aspects of diabetic retinopathy. The other classification system is aimed for use in population screening which identifies four different types of presentation of fundus disease namely, Retinopathy, maculopathy, photocoagulation and unclassifiable.

**ETDRS** has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR. This is as follows:

A. Mild NPDR: Presence of at least one microaneurysm, definition not met for B, C, D, E, or F.

B. Moderate NPDR: Hemorrhages and/or microaneurysms, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.

C. Severe NPDR: Hemorrhages and/or microaneurysms in all four quadrants, or venous beading in two or more quadrants, or IRMA in at least one quadrant, definition not met for D, E, or F.

D. Very severe NPDR: Any two or more of the changes seen in severe NPDR, definition not met for E, or F.

E. Early PDR: Presence of new vessels, definition not met for F.

F. High-risk PDR: Includes any of the following characteristics - neovascularization of disc (NVD) > 1/3 $^{rd}$ to 1/4 $^{th}$ disc diameter, NVD < 1/3 $^{rd}$ to 1/4 $^{th}$ disc diameter with vitreous/pre-retinal hemorrhage, NVE with vitreous/pre-retinal hemorrhage. High-risk characteristics (HRC) were defined by DRS, as the patient, if not treated urgently, is at a high risk of severe visual loss

**G.** Diabetic maculopathy: 3 types-focal Maculopathy- presence of micro aneurysms, hemorrhage, macular edema and hard exudates arranged in circinate pattern. Diffuse maculopathy- presence of diffuse retinal edema and thickening. Ischemic maculopathy- marked visual loss with micro aneurysms, hemorrhage, mild or no macular edema

H. Advanced eye disease: persistent vitreous hemorrhage, Tractional retinal detachment, and Neovascular glaucoma.

## COMPLICATIONS OF DIABETIC RETINOPATHY

Diabetic retinopathy can be further a cause for a variety of ocular complications.Thes can be divided into specific and non-specific

| Specific complications: | Non-specific complications |
|---|---|
| -Retinal detachment | -Glaucoma |
| -Rubeosis iridis | -Retinal vein occlusion |
| -Cataract | -Optic disc swelling |
| -maculopathy | |
| -papillopathy | |

# THE THYROID GLAND

## Anatomy of the thyroid gland

The thyroid ( Greek *thyreos*, shield, plus *eidos*, form ) is a highly vascular, brownish-red gland located anteriorly in the lower neck, extending from the level of the fifth cervical vertebra down to the first thoracic vertebra. The gland consists of a right and left part which are joined to each other by the isthmus. A third pyramidal lobe may some times project from the isthmus or one of the lobes.

Although weight of the thyroid varies, it averages 25-30 g in adults. Four parathyroid glands, which produce parathyroid hormone, are located posterior to each pole of the thyroid.

The thyroid gland has two capsules covering it. The true capsule is formed by condensation of the connective tissue of the gland while the false capsule is derived from the pretracheal layer of deep cervical fascia.

The fascia surrounding the gland firmly attach it to the cartilage rings. This attachment of the gland to the laryngoskeleton is responsible for movement of the thyroid gland and related structures during . The recurrent laryngeal nerve is closely related to the inferior thyroid artery and it is important to protect this nerve during a thyroidectomy. The nerves, one on the left and one on the right, arise from the vagus. It supplies the laryngeal muscles.

On the right hand side, the nerve hooks around the subclavian artery. On the left, the nerve passes around aortic arch. The nerves pass beneath the Berry's ligament on their way to entering the larynx.

**Histology of Thyroid gland**:

The capsule of the thyroid sends multiple septae into the substance of the gland dividing it into lobes and lobules. The structural unit of the gland are follicles which are formed by a layer of simple epithelium enclosing a colloid filled cavity. This colloid contains the precursor of thyroid hormones, an iodinated glycoprotein called iodothyroglobulin. The size of these follicles vary and they are surrounded by dense plexuses of fenestrated capillaries, lymphatics, and sympathetic nerves.

There are two major types of cells in the epithelium, the principal cells (ie, follicular) which secrete the colloid ( iodothyroglobulin) and parafollicular cells (ie, C, clear, light cells) which produce calcitonin. Parafollicular cells lie adjacent to the follicles within the basal lamina.

**Vascular anatomy of the thyroid gland**

Three arteries usually supply the thyroid gland. The superior and inferior thyroid arteries are the main arteries whereas thyroidea ima is a less consistent one. These arteries freely anastomose with one another, ipsilaterally and contralaterally. The superior thyroid artery which is a branch of the external carotid artery is located superiorly and enters the gland at the two upper poles. The artery is closely related to the external laryngeal nerve, a branch of the superior laryngeal nerve. The inferior thyroid artery arises from the thyrocervical trunk

It supplies the posterior aspect of the gland. The Thyroidea Ima Artery of Neubauer is a lower thyroid artery that may arise from the brachiocephalic artery, the arch of the aorta, or internal mammary arteries. As it often runs in front of the aorta and over the isthmus, it is liable to be cut during a tracheostomy. . The vessel is usually single but can be a paired structure.

**Venous and lymphatic drainage:**

Three pairs of veins drain the gland. The superior thyroid vein accompanies the superior thyroid artery and becomes a tributary of the internal jugular vein (IJV). The middle vein follows a direct course laterally into the IJV. The two inferior thyroid veins do not follow a uniform path . The right passes anterior to the innominate artery and drains into the right brachiocephalic vein or anterior to the trachea to the

left brachiocephalic vein. On the left side, it drains in to the left brachiocephalic vein. Occasionally, both the inferior thyroid veins form a common trunk called the thyroid ima vein, which flows into the left brachiocephalic vein.

The gland has extensive lymphatic drainage and the immediate drainage occurs to the periglandular nodes; to the prelaryngeal, pretracheal, and paratracheal. From here it goes to the mediastinal lymph nodes.

# PHYSIOLOGY OF THYROID GLAND

The principal hormone secreted by the thyroid are T3, T4 and calcitonin. Both T3 and T4 are iodine – containing aminoacids. Small amounts of reverse triiodothyronine (RT3) are also formed, but RT3 is inactive.T3 is more active than T4.

**Thyroglobulin (Tg) :**

$T_4$ and $T_3$ are synthesized in the colloid by iodination and condensation of tyrosine molecules bound in peptide linkage in Tg. This glycoprotein is made of two subunits and has a molecular weight of 660,000. It has 123 tyrosine residues, but only four to eight of these are normally incorporated into thyroid hormones. Tg is synthesized in the thyroid cells and secreted into the colloid by exocytosis of granules that also contain thyroid peroxidase (TPO). The hormones remain bound to Tg until secreted. When they are secreted, colloid is ingested by thyroid cells, the peptide bonds are hydrolyzed, and free $T_4$ and $T_3$ are discharged into the capillaries.

## Properties of thyroid hormones

| Hormone<br>Property | $T_4$ | $T_3$ |
|---|---|---|
| Serum concentrations | | |
| Total hormone | 3.2 – 12.6 microg/dl | 60-181 ng/dl |
| Fraction of total hormone in the free form | 0.025% | 0.2-0.3 % |
| Free hormone | $21 \times 10^{-12}$ *M* | $6 \times 10^{-12}$ *M* |
| Serum half-life | 5-7 d | .5 to 1 d |
| Fraction directly produced by the thyroid | 100% | 20% |
| Rate of production, including peripheral conversion | 90-100 µg/d | 30-35 µg/d |
| Intracellular hormone fraction | 20% | 70% |
| Relative metabolic potency | 0.3 | 1 |

## THYROID HORMONE SYNTHESIS

### Iodine metabolism and transport

The primary function of the thyroid gland is to produce the amount of thyroid hormone necessary to meet the demands of the peripheral tissues. This requires the daily thyroidal uptake of sufficient iodide and its oxidation by thyroid peroxidase enzyme to allow the synthesis of approximately 85 micrograms of $T_4$, which is nearly 65% iodine by weight. This requires the synthesis of a 660-kd glycoprotein homodimer, Tg. Tg contains specific tyrosine residues that are then iodinated at the apical portion of the thyroid cell to form mono- and diiodotyrosine (MIT and DIT)

TPO-catalyzed coupling of two molecules of DIT, or one of DIT and one of MIT, leads to formation of $T_4$ and $T_3$, respectively, which are then stored as colloid, still as part of the Tg molecule. Pinocytosis of stored colloid leads to the formation of phagolysosomes, the colloid droplets in which Tg is digested, releasing $T_4$, $T_3$, DIT, and MIT as the droplet is translocated toward the basal portion of the cell. Thyroxine and $T_3$ exit the cell into the capillaries, and DIT and MIT are deiodinated by an iodotyrosine deiodinase to allow recycling of the iodide to iodinate newly synthesized Tg.

Iodine deficiency is prevalent in many high altitude regions and in parts of central Africa, central South America, and northern Asia. According to the W.H.O there are nearly 2 billion iodine-deficient people in the world, based on urinary excretion data. In areas of relative iodine deficiency, there is an increased prevalence of goiter and, when deficiency is severe, hypothyroidism and cretinism. The recommended average daily intake of iodine is 150μg/d for adults around 100 for children and 180 to 200 μg per day for pregnant women.

## TSH ACTION

TSH, secreted by the anterior pituitary, is a 31-kDa hormone with alpha and a beta subunit, the alpha subunit is common to the other glycoproteins hormones (LH, FSH, hCG) whereas beta subunit is unique to TSH. TSH regulates functions of the thyroid gland through the TSH-Receptor, a seven-transmembrane G protein-coupled receptor (GPCR). The TSH-R is coupled to the alpha subunit of stimulatory G protein (Gso), which activates adenyl cyclase, leading to increased production of cyclic AMP. TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of the TSH-R is exemplified by the consequences of naturally occurring mutations. Recessive loss-of-function mutations cause thyroid hypoplasia and congenital hypothyroidism. Dominant gain-of-function mutations cause

sporadic or familial hyperthyroidism that is characterised by goiter, thyroid cell hyperplasia and autonomous function. Most of this activating mutations occur in the transmembrane domain of the receptor.

## FACTORS INFLUENCING THYROID HORMONE SYNTHESIS AND RELEASE :

### Hypothalamic-Pituitary-Thyroid Axis

The thyroid gland participates with the hypothalamus and pituitary gland in a classic feedback control loop. In addition, there is an inverse relationship between the glandular organic iodine level and the rate of hormone formation. Such auto regulatory mechanisms serve to stabilize the rate of hormone synthesis despite fluctuations in the availability of iodine. Stability in hormone production is achieved, in part, because the large intraglandular store of hormone buffers the effect of acute increases or decreases in hormone synthesis. Auto regulatory mechanisms within the gland, in turn, tend to maintain the constancy of the thyroid hormone pool.

Finally, the hypothalamic-pituitary feedback mechanism senses variations in the availability of free thyroid hormones, however small, and acts to correct them. There is a close relationship between the hypothalamus, the anterior pituitary gland, the thyroid gland, and still higher centers in the brain, with the function of the entire complex being modified in a typical negative-feedback manner by the availability of the thyroid hormones. Additional hormones and neuropeptides also influence this axis.

## EXOGENOUS AND ENDOGENOUS FACTORS THAT INFLUENCE THYROID HORMONE ECONOMY:

1) Pregnancy and maternal- fetal interactions

2) Glucocorticoids

3) Gender and gonadal steroids

4) Growth hormone

5) Environmental temperature

6) Nutrition

7) Effects of illness

## THYROID HORMONE TRANSPORT AND METABOLISM

### Serum binding proteins

T4 is secreted from the thyroid gland in about twenty fold excess over T3. Both T3 and T4 are bound to plasma proteins, including thyroxine-bimding globulin (TBG); transthyretin (TTR) and albumin. These proteins increase the pool of circulating hormone, delay renal clearance of the hormone, and may modulate hormone delivery to select tissue sites. The concentration of TBG is relatively low (1-2 mg/dl) but because of its high affinity for thyroid hormones (T4 > T3), it carries about 80% of the bound hormones. In comparison albumin has relatively low affinity for thyroid hormones but has a high plasma concentration (~3.5 g/dl), and it binds upto 10% of T4 and 30% of T3. TTR carries about 10% of T4 but little T3. When the effects of the various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T3 are protein-bound. Because T3 is less tightly bound then T4, the fraction of unbound T3 is greater than unbound T4, but there is less unbound T3 in the circulation because it is produced in smaller amounts and cleared more rapidly than T4. The unbound, or free concentrations of the hormones are ~2 X $10^{-11}$M for T4 and ~6 X $10^{-12}$M for T3, which roughly correspond to the thyroid hormone receptor bindinf contants for these hormones. The unbound hormone is thought to be biologically available to tissues, although the discovery of megalin as a cellular transporter of protein-bound steroids raises the possibility

of distinct transport systems for bound and unbound hormones. Nonetheless, the homeostatic mechanism that regulate the thyroid axis are directed toward maintenance of normal concentrations of unbound hormones.

**Deiodinaes**

T4 may be thought of as a precursor for the more potent T3. T4 is converted to T3 by the deiodinase enzymes. Type 1 deiodinase, which is located primarily in thyroid, liver, and kidney has a relatively low affinity for T4. Type 2 deiodinase has a higher affinity for T4 and is found primarily in the pituitary gland, brain, brown fat, and thyroid gland. Expression of type 2 deiodinase allows it to regulate T3 concentrations locally, a property that may be important in the context of levothyroxine (T4) replacement. Type 2 deiodinase is also regulated by thyroid hormone; hypothyroidism induces the enzyme, resulting in enhanced T4→T3 conversion in tissues such as brain and pituitary. T4→T3 conversion is impaired by fasting, systemic illness or acute trauma, oral contrast agents, and a variety of medications (e.g. propylthiouracil, propranolol, amiodarone, glucocorticoids). Type 3 deiodinase inactivates T4 and T3 and is the most important source of reverse T3 (rT3). Massive hemangiomas that express type 3 deiodinase are rare cause of hypothyroidism in infants.

## THYROID HORMONE ACTION:

Circulating thyroid hormones enter cells by passive diffusion and via the monocarboxylate 8 (MCT8) transporter. After entering cells, thyroid hormones act primarily through nuclear receptors, although they also stimulate plasma membrane and mitochondrial enzymatic responses. Thyroid hormones bind with high affinity to nuclear *thyroid hormone receptors* (TRs) α and β.TR α is particularly abundant in brain, kidney, gonads, muscle, and heart, whereas TR β expression is relatively high in the pituitary and liver. However, structural differences in the ligand binding domains provide the potential for developing receptor-selective agonists or antagonists. $T_3$ is bound with 10–15 times greater affinity than $T_4$, which explains its increased hormonal potency. Though $T_4$ is produced in excess of $T_3$, receptors are occupied mainly by $T_3$, reflecting $T_4 \rightarrow T_3$ conversion by peripheral tissues, greater $T_3$ bioavailability in the plasma, and receptors' greater affinity for $T_3$.

## EFFECTS OF THYROID HORMONES :

Many of the various effects of thyroid hormones in the body are secondary to stimulation of oxygen consumption ( calorigenic action ). The hormones also affect growth and development in mammals, help regulate lipid metabolism, and increase the absorption of carbohydrates from the intestine. They also increase the release of oxygen from hemoglobin by increasing red cell 2,3-DPG.

PHYSIOLOGIC EFFECTS OF THYROID HORMONES

| **Target tissue** | **Effect** | **Mechanism** |
|---|---|---|
| Heart | Chronotropic | Enhances number and affinity of β-adrenergic receptors |
| Heart | Inotropic | Increases responses to circulating catecholamines. Increases proportion of α-myosin heavy chain |
| Adipose tissue | Catabolic | Stimulate lipolysis |
| Muscle | Catabolic | Increase protein catabolism |
| Skeletal system | Developmental | Promotes normal growth and skeletal development |
| CNS | Developmental | Promote normal brain |
| Lipoprotein | Metabolic | Increased number of LDL receptors |
| Others | Calorigenic | Increases oxygen consumption metabolically active tissues |

## EVALUATION OF THYROID DISORDERS

Diseases of the thyroid gland almost always manifest themselves with symptoms resulting from either excessive or insufficient production of thyroid hormone. The thyroid disease is established on the clinical grounds and the functional disturbance is assessed by the metabolic state. The functional diagnosis of thyroid disease is based upon a carefully taken history, through search for the physical signs of hypo or hyperthyroidism and in an elegant appraisal of the results of the laboratory tests

CLINICAL FEATURES OF THYROID DISORDERS

## HYPOTHYROIDISM

### Symptoms

Tiredness, Weakness, Dry skin

Feeling cold, Hair loss

Poor concentration and memory

Constipation,

Weight gain with poor appetite,

Dyspnea

Hoarse voice

Menorrhagia

(later oligomenorrhea or amenorrhea)

Paresthesia , Impaired hearing

### Signs

Dry coarse skin; cool extremities

Puffy face, hands, and feet (myxedema)

Diffuse alopecia

Bradycardia

Peripheral edema

Delayed tendon reflex relaxation

Carpal tunnel syndrome

Serous cavity effusions

## HYPERTHYROIDISM

**Symptoms**

Hyperactivity,Irritability

Increased sweating

Fatigue and weakness

Palpitation

Oligomenorrhea and loss of libdo

Weight loss with increased appetite

Diarrhea, Polyuria

**Signs**

Tachycardia, Atrial Fibrillation

Tremor

Goiter

Warm moist skin

Proximal myopathy

Lid Retraction

Gynaecomastia

## SUB CLINICAL HYPOTHYROIDISM

Defined as an elevated TSH levels with normal free thyroxine levels , among people without any history of thyroid disorders .Subclinical hypothyroidism has a prevalence of around 5%. The prevalence is higher in the elderly and females. Above 60 years, the prevalence is nearly equal in males and females, with a combined prevalence of around 10%. Nearly 80% of these patients have anti thyroid anti bodies in their serum and their TSH values are usually less than 10mIU/ml. Before diagnosing SCH, other causes of an elevated TSH level, such as convalescence, variability in assay, presence of heterophile antibodies that can affect the results, and some cases of central hypothyroidism with biologically inactive TSH and thyroid hormone resistance, need to be ruled out. Autoimmune disordere of the thyroid are the most common cause of elevated TSH. Surgeries, radiation exposure and radio iodine therapy can also lead on to mild thyroid failure. SCH may develop in the post partum period and after episodes of silent and De Quervain's thyroiditis.

## Defining the normal upper limit level for serum TSH level:

Even though people with a TSH level between 3.0 and 5.0 mIU/L are more likely to have positive antithyroid antibodies and future thyroid disease, the lack of evidence for a benefit from levothyroxine therapy at these levels makes keeping the upper limit of TSH at 4.0 to 5.0 (depending on the laboratory) more reasonable. In the elderly population (>70 years) hypothyroidism need not be diagnosed even with TSH values up to 7 mIU/ml in the absence of anti-thyroid antibodies. Similarly normal TSH values for pregnancy are different.

## Screening for SCH:

The American Thyroid Association recommends screening by measurement of serum TSH beginning at age 35 years and every 5 years thereafter. The American College of Physicians acknowledges that treatment for subclinical thyroid dysfunction is controversial but suggests that screening to detect thyroid dysfunction may be indicated in women older than 50 years.Screening is advised much more aggressively in the pregnant population due to the adverse effects of SCH on the fetus ans well as the outcome of the pregnancy.

## Adverse consequences of SCH

Although studies have pointed to some adverse effects of SCH, no consensus exists as to the clinical importance of the adverse effects and the benefits of levothyroxine therapy, particularly for the 80% of patients with SCH who have a TSH of less than 10 mIU/L, because of the different levels of TSH and degrees of thyroid dysfunction in these studies.

## Progression to overt hypothyroidism

The annual rate of progression of SCH to overt hypothyroidism is quite high (2.6%).This is even higher if thyroid peroxidase antibody is positive (4.3%).

However some people do not show progression and some even show normalization of TSH values. People with a higher value of TSH (>10miu/l) show a higher rate of progression while those with a lower value(<6 miu/l) are less likely to progress.

## THYROID FUNCTION TEST

The principal value of these tests is in assessing the thyroid status when the clinical picture is equivocal. However, even if clinical diagnosis appears quite certain it is valuable to have confirmatory evidence. Several parameters should be obtained because no single test is conclusive. These tests are used in the investigations of the patient with doubtful toxicity, in the diagnosis of hypothyroidism .

**THYROID FUNCTION TEST CAN BE CLASSIFIED AS FOLLOWS**

1)Blood test

2)Non Blood test

TSH, T4, T3 and Free T4 are the blood tests which are widely used and readily available. To evaluate thyroid function following test are done:

## TSH Tests

Measuring TSH level in blood sample is the best initial test for thyroid function. A direct problem in thyroid (primary hypothyroidism) is suggested by a raised TSH level. The opposite happens in hyperthyroidism where there is low levels of TSH indicating an overactive thyroid producing excess of thyroid hormones. Occasionally pituitary gland abnormality will result in low levels of TSH which will then result in thyroid dysfunction (secondary hypothyroidism). A normal TSH level indicates that the thyroid is normally functioning in most healthy individuals.

## T4 Tests

Two forms of T4 circulates in the blood: 1)Protein bound T4 prevents T4 from entering metabolically active tissues requiring thyroid hormones and 2) free T4, which exerts its action after entering the various. Thyroid function cannot be determined without taking the free T4 fraction, and tests which measure this are called the Free T4 index(FT4I or FTI) and the Free T4 (FT4). An elevated levels of free T4 or free T4 index will be seen in individuals with hyperthyroidism, whereas low levels of free T4 or free T4 index will be seen in individuals with hypothyroidism. Thyroid gland fuction can be accurately determined by combining the TSH levels and free T4 or free T4 index. Primary hypothyroidism because of disease in thyroid gland is indicated by elevated

TSH levels and low free T4 levels or low free T4 index. Hypothyroidism secondary to disease in pituitary gland is indicated by low TSH and low free T4 levels or low free T4 index. Individuals with hyperthyroidism will have lowTSH levels and an elevated free T4 levels or low free T4 index.

T3 Tests

For diagnosis of hyperthyroidism or to assess the severity of hyperthyroidism blood levels of T3 are very useful. An elevated T3 levels will be seen in hyperthyroid individuals. Only an elevated T3 levels with a normal free T4 or free T4 index will be seen in some individuals with low TSH levels. T3 becomes abnormal last in individuals with hypothyroidism,so rarely used for diagnosis of hypothyroidism. Even patients with severe hypothyroidism with a raised TSH levels and low free T4 levels or low free T4 index can have a normal T3 test. During pregnancy or females on birth control pills, raised levels of T4 or T3 can be seen due to increased protein binding because of estrogen hormone. In these situations,TSH levels and free T4 or free T4 index should be done for thyroid function.

## Thyroid Antibody Tests

Thyroid dusfunction caused by two antibodies that are directed against thyroid cell proteins: thyroid peroxidase and thyroglobulin. Measurement of thyroid antibody levels can help to diagnose thyroid problems. For example, Hashimoto's thyroididtis can be diagnosed by positive anti-thyroid peroxidase and/or anti-thyroglobulin antibody levels in a patient with hypothyroidism. Autoimmune thyroid disease can be diagnosed if the antibodies are positive in a hyperthyroid patient.

## Thyroglobulin

Normal thyroid gland and also thyroid cancer cells produce a protein called Thyroglobulin (Tg). In patients with intact thyroid gland,it does not measure thyroid function and it does not diagnose thyroid cancer. It is used to monitor patients after treatment of thyroid cancer who have undergone thyroidectomy.

## NON-BLOOD TESTS

Radioactive iodine uptake

The thyroid gland must extract a large amount of iodine out of the blood stream so that the gland can incorporate appropriate amount of iodine in T4. A very active mechanism is present in the thyroid gland for carrying out this function. By asking patients to swallow a small amount of radioactive iodine this active mechanism can be assessed to measure thyroid function. The radioactivity helps to track where the iodine molecules go. One can assess whether the thyroid gland is functioning normally or not, by measuring the amount of radioactivity taken up by the thyroid gland (radioactive iodine uptake, RAIU). When the thyroid gland is overactive(hyperthyroidism), a very high RAIU will be seen in individuals while a low RAIU will be seen when the thyroid gland is underactive (hypothyroidism).

In addition to the above tests, a thyroid scan may be done, which shows a picture of the thyroid gland.

## PREVALENCE OF THYROID DISORDERS IN DIABETES MELLITUS

It is known that Diabetes and thyroid diseases influence each other mutually. Several reports suggest a higher than normal prevalence of thyroid dysfunction among diabetics. This was found to be more common in patients suffering from Type 1 Diabetes than among Type 2 Diabetics.

This is understandable as both conditions have auto immunity as a common underlying mechanism. In addition, positive TPO anti bodies have been reported in as many as 38% 0f Diabetic patients and this has been shown to predict the development of sub clinical hypothyroidism.

Even in Type 2 Diabetes the association is significant. Previous studies show a prevalence varying from 6.6% to 13.4%.

The possible mechanisms by which Diabetes influences Thyroid status are:

1. In diabetics, the nocturnal TSH peak is blunted or abolished and the TSH response to TRH is impaired.

2. Reduced T3 levels have been noted in patients with uncontrolled Diabetes. This could be explained due to reduced peripheral conversion of $T_4$ to$T_3$.

## EFFECTS OF THYROID DYSFUNCTION ON DIABETES

The different mechanisms by which thyroid dysfunction affect the Diabetes status are:

1. Thyroid dysfunction, both hypothyroididsm and hyperthyroidism are associated with increased insulin resistance.

2. In hypothyroidism the renal clearance of insulin is decreased resulting in reduced insulin requirements.

3. The loss of appetite seen in hypothyroidism contributes to decreased insulin requirements.

4. Hypothyroid patients especially Type 1 Diabetics have a reduced rate of gluconeogenesis hence these patient have an increased incidence of hypoglycemia.

5. Even subclinical hypothyroidism has a negative impact on lipid metabolism and it is an independent risk factor for myocardial infarction and retinopathy

6. Another possible mechanism linking SCH to vascular diseases is the finding that thyroid hormones inhibit collagen induced platelet aggregation and directly relax smooth muscles.

7. Further hypothyroidism is accompanied by a hypercoagulable state and increased blood viscosity.

Thus presence of associated thyroid dysfunction has significant implications when it comes to glycemic control, insulin resistance, glycemic control and complications of Diabetes.

Patients with associated hypothyroidism have been noted to have a higher incidence of microvascular complications especially nephropathy and retinopathy. These patients have a higher risk of having much more severe retinopathy too. The effects of hypothyroidism on platelet function and its rheological effect are said to play an important role in this regard.

A higher prevalence of thyroid dysfunction (especially SCH) has been noted in the south and south east-asians having Type 2 DM. Screening with TSH measurement is not expensive. However, the cost-effectiveness of screening diabetic patients for thyroid dysfunction is likely to depend on a number of factors like local prevalence, ethnicity, as well as on the question of whether sub-clinical hypo- and hyperthyroidism should be treated, which itself is not fully resolved.

## EFFECTS OF THYROID HORMONES ON PATHOGENESIS OF DIABETIC RETINOPATHY

Numerous factors have been implicated in the pathogenesis of retinal new vessels, including erythropoietin, growth hormone, basic fibroblast growth factor (bFGF), insulin-like growth factor 1 (IGF-1), and VEGF.

Other class of molecules involved in pathogenesis of retinal new vessels other than growth factors include integrins which act as specific extracellular matrix proteins. Integrin αvβ3 is usually not expressed on microvessels but is increased in response to angiogenic stimulation. New vessels in ocular tissue from patients with diabetic retinopathy especially proliferative diabetic retinopthy have shown selective upregulation of integrin αvβ3 and αvβ5.

Integrin αvβ3 is an important regulator of angiogenesis. Various studies have shown that pharmacologic inhibition of this integrin blocks new vessels in multiple animal models.

Integrin αvβ3 has pro – angiogenic effects on various growth factors including vascular endothelial growth factor (VEGF). On stimulation with VEGF, it interats with vascular endothelial growth factor receptor 2 (VEGFR2) and forms a complex with VEGFR2. Inhibition of integrin αvβ3 results in decreased VEGFR2 autophosphorylation and signalling.

The molecular mechanism for pro - angiogenic of thyroid hormones is genomic and nongenomic. It is initiated non - genomically by integrin. Integrin αvβ3 has cell surface receptor site for thyroid hormone for L – thyroxine (T4) that mediates pro - angiogenic action of thyroid hormones. Kinase transduction of the thyroid hormone signal and finally transcription of many angiogenic genes result.

In a study by Takeshi Yoshida et al, inhibition of retinal neovascularisation by the integrin αvβ3 antagonist tetraiodothyroacetic acid (tetrac) has been documented.

Integrin αvβ3 is a promising therapeutic target for retinal neovascularization and for modulating the pro – angiogenic activity of growth factors.

# PART TWO:

## AIMS AND OBJECTIVES

1. To assess the prevalence of Thyroid dysfunction among Type 2 DM patients.

2. To assess the prevalence of retinopathy among Type 2 Diabetes patients.

3. To assess whether thyroid dysfunction is associated with increased risk of retinopathy in type 2 diabetes patients.

## MATERIALS AND METHODS

STUDY DESIGN:

This is a case control study.

This study was conducted among 100 Type 2 DM patients attending the OP as well as in the wards at Govt.Rajaji.Hospital Madurai.

Subjects were evaluated for entry into the study if they are 12 years of age or older. Subjects believed to fulfill all eligibility criteria, and none of the exclusion criteria, were invited to participate in the study.

STUDY PERIOD:

9 Months ( April 2014 to August 2014 )

SELECTION OF STUDY SUBJECTS:

A total of 100 patients attending the O.P units and in the wards of the department of Ophthalmology, Government Rajaji Hospital Madurai who satisfy the inclusion criteria

INCLUSION CRITERIA:

1. Patients diagnosed with Type 2 Diabetes on treatment.
2. Duration>5 years of diabetes mellitus.
3. Age>12 yrs

EXCLUSION CRITERIA:

1. Patients with known history of thyroid disorder.
2. Patients on drugs known to affect thyroid function like Lithium , Amiodarone, oral contraceptive pills, e.t.c.
3. Pregnant Patients.
4. Patients in whom fundus cannot be examined.
5. Patients not consenting for the study.
6. Systolic BP>140 and Diastolic BP>90.
7. Glaucoma patients.
8. Nephropathy patients.

DATA AND SAMPLE COLLECTION:

Data and Blood samples will be collected from established cases of type two diabetes patients on treatment from which serum shall be extracted for Thyroid Profile.

ASSESSMENT OF THYROID PROFILE:

The Thyroid Profile will be estimated from the serum samples of the selected patients by Elisa technique at the endocrinology department. T3 T4 and TSH levels will be estimated.

Normal thyroid profile:

| Test | Abbreviation | Typical Ranges |
|---|---|---|
| Serum thyroxine | T4 | 4.6-12ug/dl |
| SerumTriiodothyronine | T3 | 80-180 ng/dl |
| Seruthyroid stimulating hormone. | TSH | 0.5-6uIU/ml |

The following guidelines for detection of thyroid dysfunction were considered –

- Normal – when T3, T4 and TSH were within the normal range.
- Primary hypothyroidism – when TSH is more than 6 μIU/ml and T3, T4 is less than the normal value.
- Primary hyperthyroidism --when TSH is less than 0.5 μIU/ml and T3, T4 is more than the normal values.
- Subclinical hypothyroidism – when TSH is more than 6 μIU/ml and T3, T4 is within the normal range.
- Subclinical hyperthyroidism – when TSH is less than 0.5 μIU/ml and T3, T4 are within the normal range.

ASSESSMENT OF RETINOPATHY:

All the study patients will be assesssd by an ophthalmologist for a detailed ocular examination for detection and grading of retinopathy. The prevalence of hypothyroidism in patients with and without diabetic retinopathy will be analyzed.

**ETDRS** has classified NPDR into mild, moderate, severe and very severe and PDR into early PDR and high-risk PDR. This is as follows:

**A**. Mild NPDR: Presence of at least one microaneurysm, definition not met for B, C, D, E, or F.

**B**. Moderate NPDR: Hemorrhages and/or microaneurysms, presence of soft exudates, venous beading, IRMA definitely present, definition not met for C, D, E, or F.

C. Severe NPDR: Hemorrhages and/or microaneurysms in all four quadrants, or venous beading in two or more quadrants, or IRMA > standard photo 8A in at least one quadrant, definition not met for D, E, or F.

D. Very severe NPDR: Any two or more of the changes seen in severe NPDR, definition not met for E, or F.

E. Early PDR: Presence of new vessels, definition not met for F.

F. High-risk PDR: Includes any of the following characteristics - neovascularization of disc (NVD) > 1/3 $^{rd}$ to 1/4 $^{th}$ disc diameter, NVD < 1/3 $^{rd}$ to 1/4 $^{th}$ disc diameter with vitreous/pre-retinal hemorrhage, NVE with vitreous/pre-retinal hemorrhage. High-risk characteristics (HRC) were defined by DRS, as the patient, if not treated urgently, is at a high risk of severe visual loss

**G.** Diabetic maculopathy: 3 types-focal Maculopathy- presence of micro aneurysms, hemorrhage, macular edema and hard exudates arranged in circinate pattern. Diffuse maculopathy- presence of diffuse retinal edema and thickening. Ischemic maculopathy- marked visual loss with micro aneurysms, hemorrhage, mild or no macular edema

H. Advanced eye disease: persistent vitreous hemorrhage, Tractional retinal detachment, and Neovascular glaucoma.

## OBSERVATIONS AND STATISTICAL ANALYSIS

### DESCRIPTIVE ANALYSIS

Age Distribution

The age of the patients studied varied from 37 years to 78.

**AGE**

| Age group | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| 35-45 | 12 | 12.0 | 12.0 | 12.0 |
| 45-55 | 37 | 37.0 | 37.0 | 49.0 |
| 55-65 | 36 | 36.0 | 36.0 | 85.0 |
| 65-75 | 13 | 13.0 | 13.0 | 98.0 |
| 75-85 | 2 | 2.0 | 2.0 | 100.0 |
| Total | 100 | 100.0 | 100.0 | |

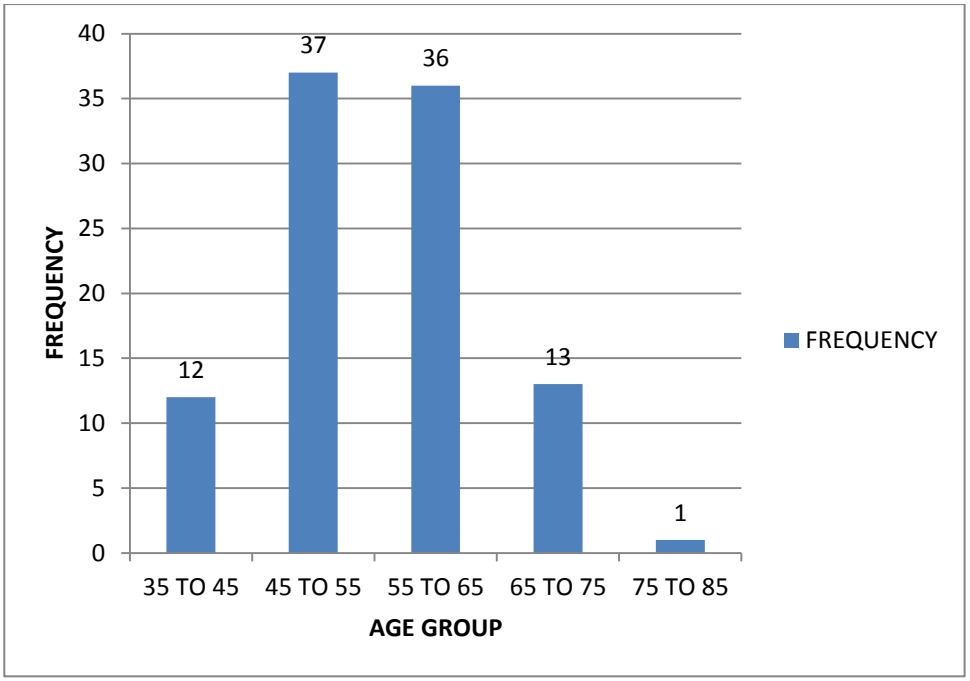



Figure 1 Bar diagram showing age distribution of study population

## SEX DISTRIBUTION

Among the 100 patients 50 were males and 50 females.

**SEX**

| | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| Females | 50 | 50.0 | 50.0 | 50.0 |
| Males | 50 | 50.0 | 50.0 | 100.0 |
| Total | 100 | 100.0 | 100.0 | |

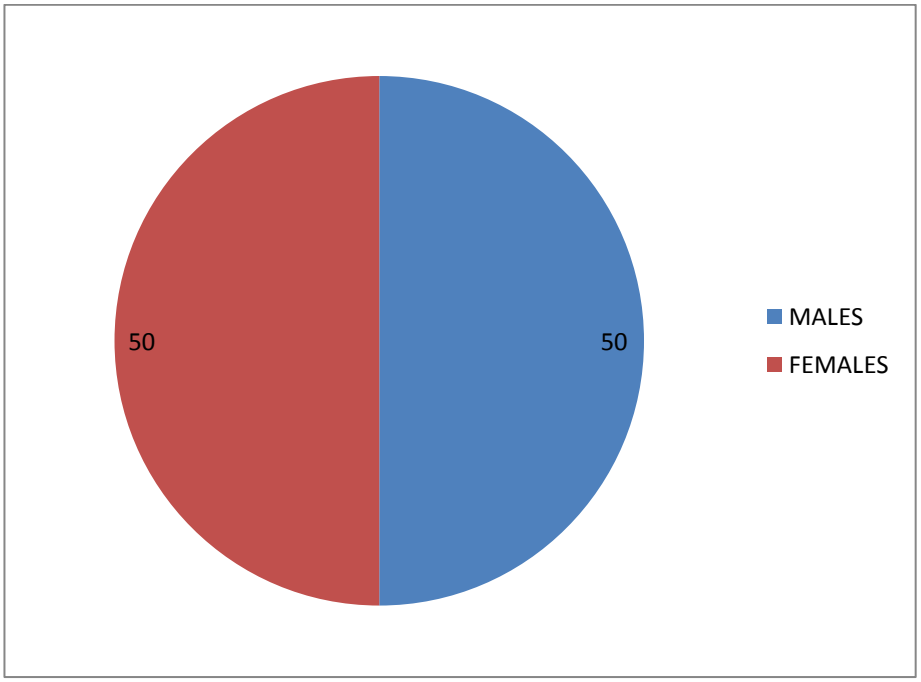



Figure 2 Pie chart showing sex distribution of study population

## DURATION OF DIABETES

The study group had an duration of Diabetes of minimum 5 years and a maximum of 20 years.

**DURATION**

| | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| 5-10 | 72 | 72 | 72.0 | 72.0 |
| 10-15 | 19 | 19.0 | 19.0 | 91.0 |
| 15-20 | 9 | 9.0 | 9.0 | 100.0 |
| Total | 100 | 100.0 | 100.0 | |

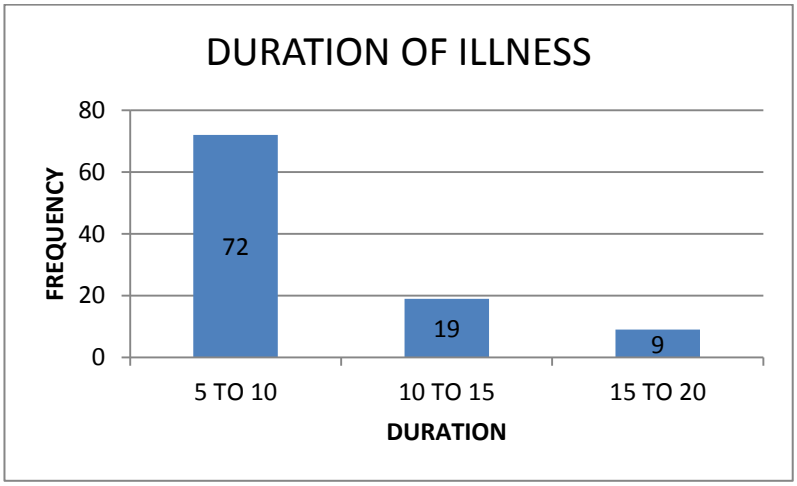



Figure 3 Bar Diagram showing duration of illness in study population

SEX DISTRIBUTION OF THYROID DYSFUNCTON AMONG THE PATIENTS

| SEX | THYROID DYSFUNCTON | | | |
|---|---|---|---|---|
| | PRESENT | | ABSENT | |
| | NUMBER | PERCENTAGE | NUMBER | PERCENTAGE |
| MALES | 7 | 14% | 43 | 86% |
| FEMALES | 16 | 32% | 34 | 68% |

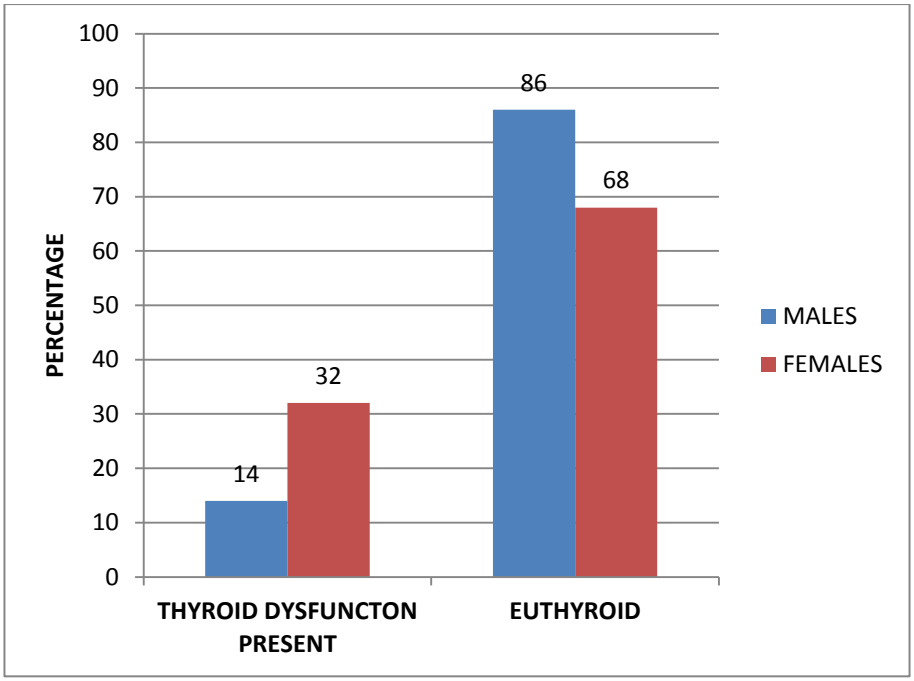



Figure 4 Bar Diagram depicting sex distribution of thyroid dysfunction

## SEX DISRIBUTION OF RETINOPATHY

| SEX | RETINOPATHY | | | |
|---|---|---|---|---|
| | PRESENT | | ABSENT | |
| | NUMBER | PERCENTAGE | NUMBER | PERCENTAGE |
| MALES | 28 | 56% | 22 | 44% |
| FEMALES | 22 | 44% | 28 | 56% |

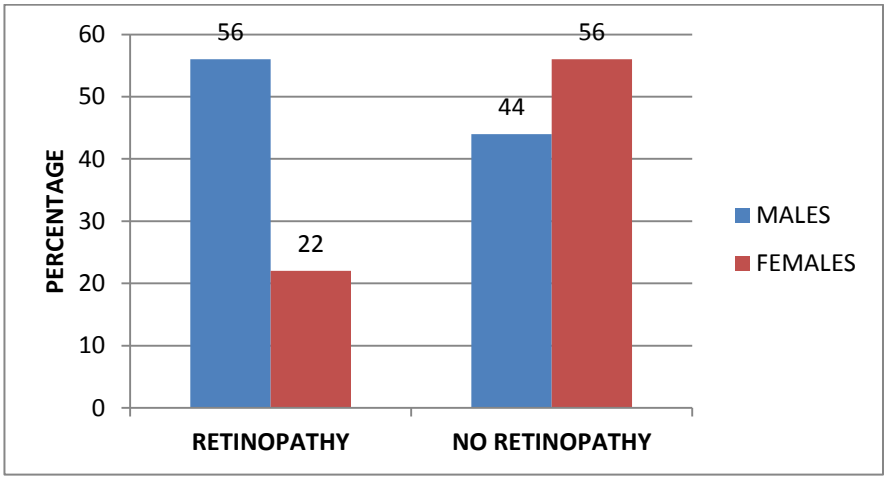



Figure 4 Bar Diagram depicting sex distribution of retinopathy

## RELATIONSHIP OF RETINOPATHY & DURATION OF ILLNESS

| DURATON | NUMBER OF PATIENTS | NUMBER OF PATIENTS WITH RETINOPATHY | PREVALENCE |
|---|---|---|---|
| 5-10 | 72 | 36 | .500 |
| 10-15 | 19 | 9 | .578 |
| 15-20 | 9 | 3 | .4 |

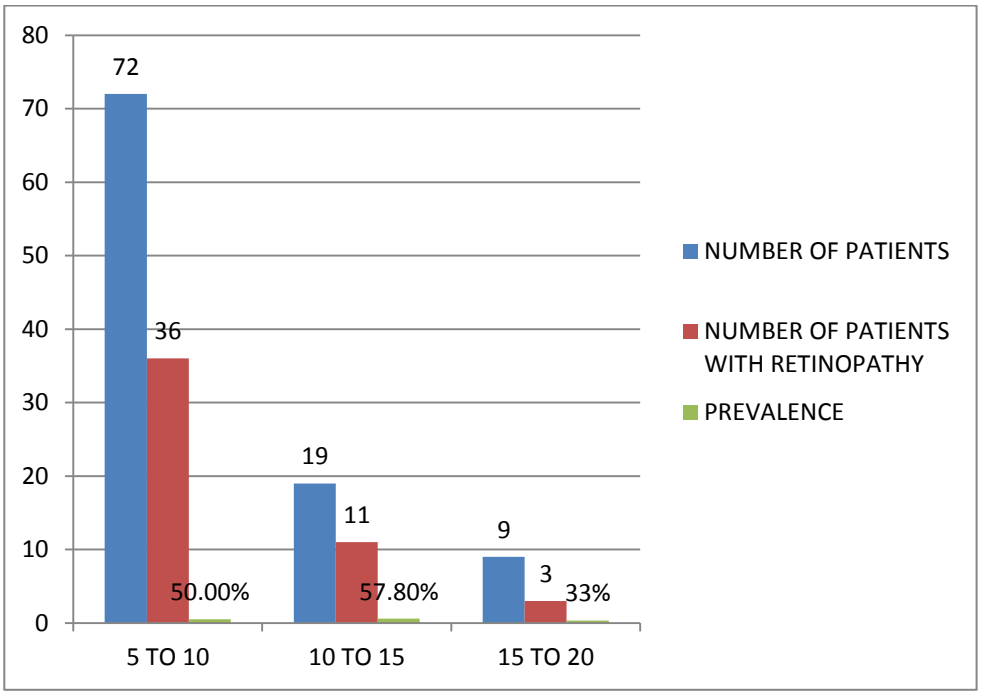



Figure 5 Bar diagram depicting relationship between retinopathy and duration of Diabetes.

## PREVALENCE OF THYROID DYSFUNCTION

Out of the 100 patients with diabetes 23 had thyroid dysfunction, the most common being sub-clinical hypothyroidism which was seen in 21 patients.2 patients had frank hypothyroidism.

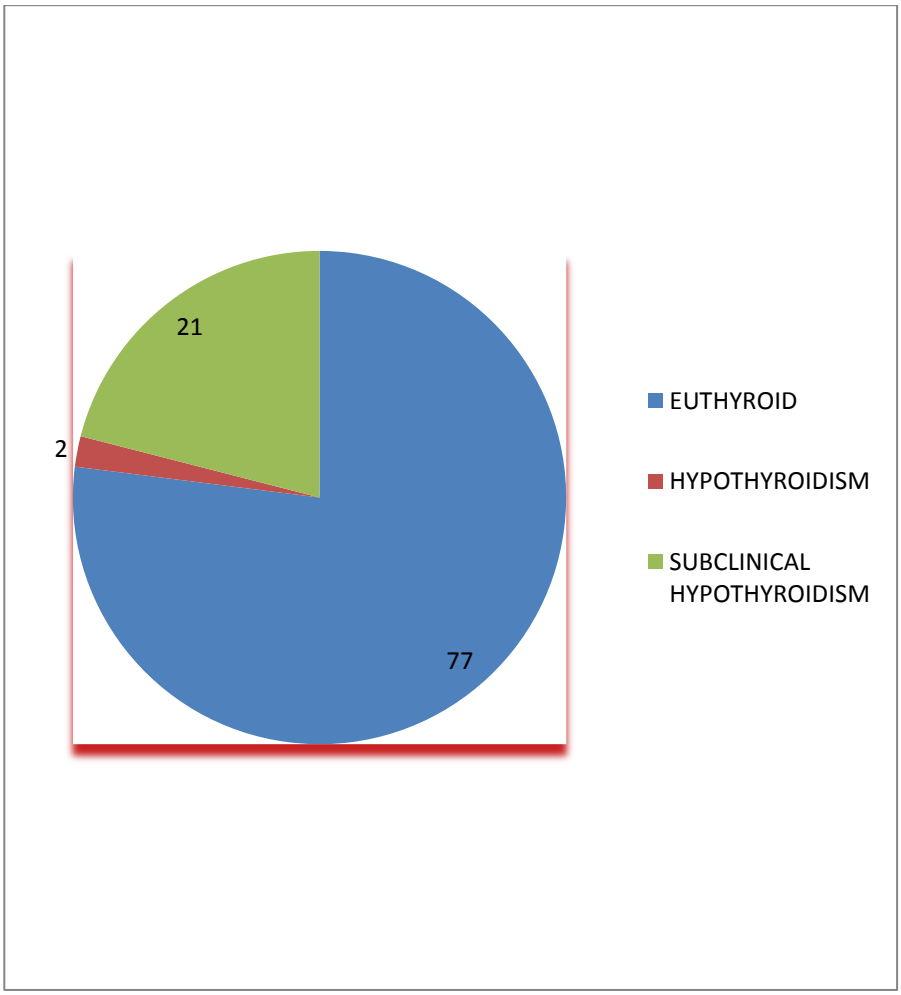



Figure 6 Pie chart depicting distributon of thyroid dysfuncton in study populaton

## PREVALANCE OF RETINOPATHY

Among the 100 patients studied 50 had diabetic retinopathy. Of which 46 had NPDR while 4 had PDR.

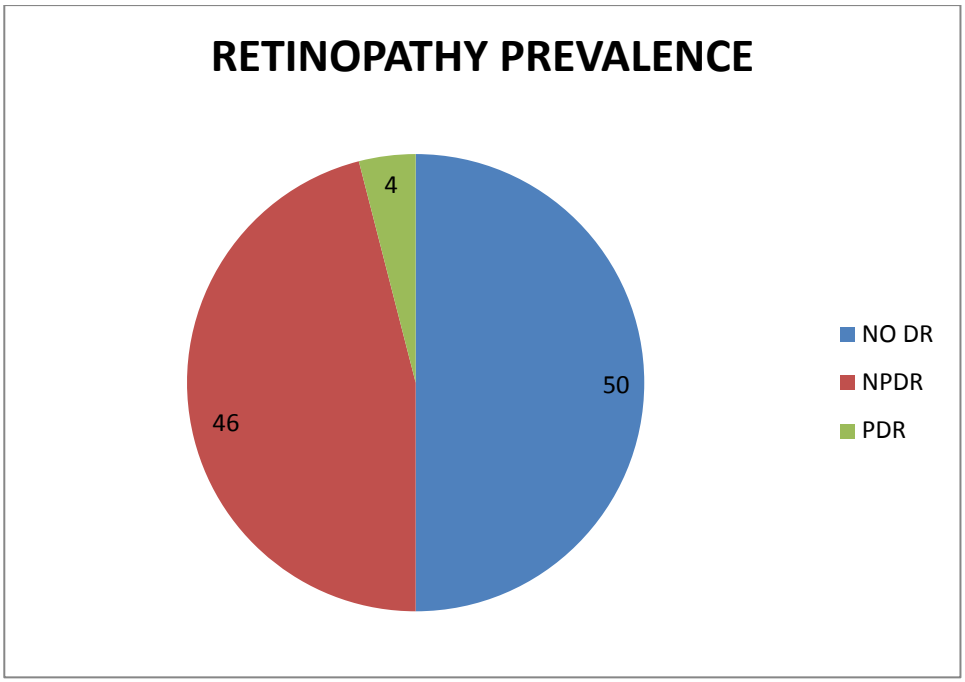



Figure 8 Pie chart depicting distribution of retinopathy in the study population

## ASSOCIATION BETWEEN RETINOPATHY AND THYROID DYSFUNCTION

Among the 50 patients with retinopathy 18 had some form of thyroid dysfunction while among the remaining 50 patients without retinopathy it was seen in 5.

| THYROID DYSFUNCTION | | RETINOPATHY PRESENT | | RETINOPATHY ABSENT |
|---|---|---|---|---|
| | | NPDR | PDR | |
| PRESENT | SCH | 15 | 01 | 05 |
| | HYPO | 01 | 01 | 00 |
| ABSENT | | 30 | 02 | 45 |

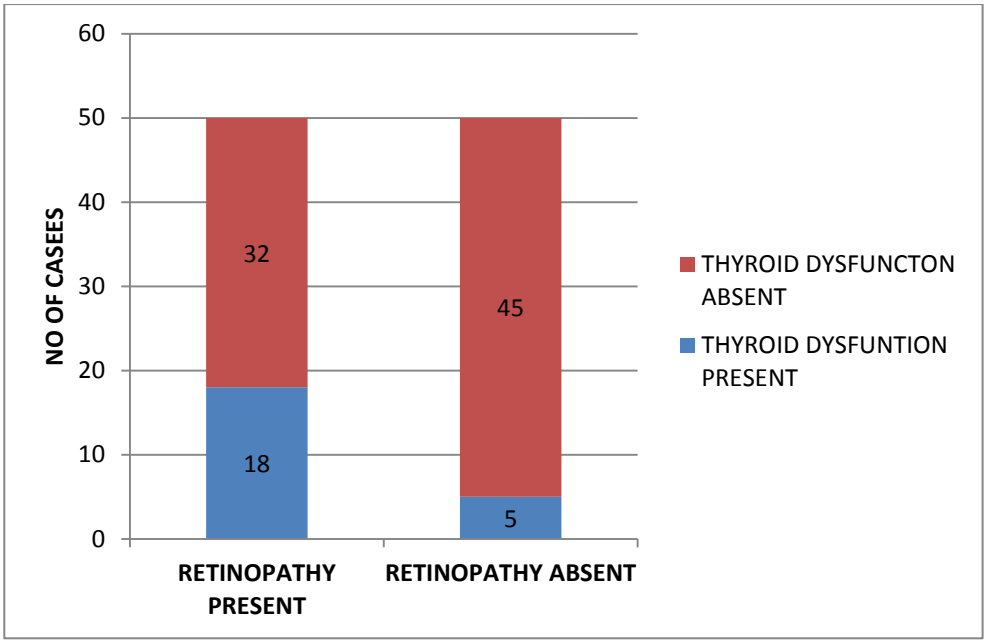



Figure 9 Bar diagram depicting association between retinopathy and thyroid dysfunction

# STASTICAL ANALYSIS

## ODD'S BASED ESTIMATE AND CONFIDENCE LIMITS

Odds ratio (OR) is a measure of the association between a risk factor ( exposure) and a disease( outcome) applied in case control studies.

An OR>1 means exposure is associated with higher odds of outcome

Confidence limits or intervals (CI) are used to measure the precision of the Odds Ratio .A large CI indicates less precision while a small CI indicates high precision for the OR.

Thus in the current study the Odds Ratio came out to be 5.06 with an upper 95% confidence limit of 15.051 and a lower confidence limit of 1.703.

Which means the odds of a Diabetic patient with thyroid dysfunction ( sub clinical and overt hypothyroidism) developing retinopathy is 5.06 times that of a Diabetic patient without thyroid dysfunction developing the same.

## TEST OF SIGNIFICANCE

In order to test the significance of above described association between thyroid dysfunction, considered the risk factor, and retinopathy, the disease, Chi Square statistic was applied.

The categorical data was displayed in a 2x2 contingency table.

| THYROID DYSFUNCTION | | DISEASE | | TOTAL |
|---|---|---|---|---|
| | | RETINOPATHY PRESENT | RETINOPATHY ABSENT | |
| EXPOSURE | PRESENT | 18 | 05 | 23 |
| | ABSENT | 32 | 45 | 77 |
| TOTAL | | 50 | 50 | 100 |

- The test statistic is:

$$c^2 = \sum_{i=1}^{k} \left[ \frac{(O_i - E_i)^2}{E_i} \right]$$

- The degrees of freedom are:
  - $(r-1)(c-1)$
  - r = # of rows and c = # of columns
- Where:
  - $O_i$ = the observed frequency in the $i^{th}$ cell of the table
  - $E_i$ = the expected frequency in the $i^{th}$ cell of the table

An easier formula for a 2x2 table is:

- Suppose:

| | Disease | | |
|---|---|---|---|
| Exposure | Yes | No | Total |
| **Yes** | a | b | a+b |
| **No** | c | d | c+d |
| **Total** | a+c | b+d | n |

- Then we can write:

$$\chi_1^2 = \frac{n(ad-bc)^2}{(a+c)(b+d)(a+b)(c+d)}$$

| THYROID DYSFUNCT-ION | RETINOPATHY PRESENT | RETINOPATHY ABSENT | TOTAL |
|---|---|---|---|
| PRESENT | 18 | 05 | 23 |
| ABSENT | 32 | 45 | 77 |
| TOTAL | 50 | 50 | 100 |

We get a chi square value of

$$\frac{100\{(18x45)-(32x05)\}^2}{50x50x23x77} = \mathbf{9.543}$$

Comparing with the log tables this value corresponds to a P-value of < .005 which means the association between the risk factor and disease is not just by chance and is significant.

## DISCUSSION

IN OUR STUDY

| ODDS RATIO | 95% CONFIDENCE INTERVAL | P-VALUE |
|---|---|---|
| 5.06 | 1.703 – 15.051 | <0.005 |

According to this study the prevalence of thyroid dysfunction among the 100 Type 2 Diabetes Mellitus patients studied was 23% with the most common problem being sub-clinical hypothyroidism(SCH) at 21% among the study population followed by overt hypothyroidism at 2%. As expected the prevalence of thyroid dysfunction among females (32%) was much more than among males (14%).

These results are in tune with those obtained from previous similar studies. In an Indian study conducted at D Y Patil Medical College Mumbai by Vinu Vij et al. an increased prevalence of Hypothyroidism was noted among Type 2 DM patients and it was found to adverse effect on retinopathy.

In another study published in "Advances in Bio Research Volume 2, Issue 2, December 2011" authored by Gurjeet Singh et al. the thyroid profile in 80 type 2 diabetic patients was, compared with 80 non-diabetic patients. The level of $T_3$, $T_4$, $FT_3$ and $FT_4$were significantly lower while the level of TSH was

significantly higher in type 2 diabetics as compared to non-diabetics. From the 80 diabetic subjects studied, 30% showed abnormal thyroid hormone levels (23.75% had hypothyroidism including SCH and 6.25% had hyperthyroidism). Significantly higher levels of FPG, HbA1c, serum cholesterol, serum triglyceride, LDLVLDL, blood urea, creatinine, SGOT, SGPT and significantly lower level of HDL was observed in diabetics as compared to non-diabetics subjects

In a study by Diez jj et al[8] (Exp clin Endocrinol Diabetes 2011 April) 318 patients with Diabetes mellitus were evaluated for thyroid dysfunction.The number of patients with thyroid dysfunction and their respective prevalence were: overt hyperthyroidism, 11 (3.5%); subclinical hyperthyroidism, 10 (3.1%); overt hypothyroidism, 48 (15.1%), and subclinical hypothyroidism, 34 patients (10.7%). The screening program detected the following cases of newly diagnosed thyroid dysfunction: subclinical hyperthyroidism, 5 (1.6%); overt hypothyroidism, 6 (1.9%), and subclinical hypothyroidism, 20 patients (6.3%).

Comparing to the above study the prevalence of SCH and hypothyroidism were similar.

Coming to the association between thyroid dysfunction and retinopathy, our study showed a significant association between SCH and overt hypothyroidism and retinopathy in the study population, with a odds ratio of 5.06 and a P-value of <0.005.

JIN-KUI YANG et al studied 1170 Type 2 DM patients and they too found this association to be significant. They also concluded that hypothyroidism is a risk factor for more severe sight threatening proliferative retinopathy.

In a Korean study by Bo-Yeon Kim et al 637 patients with Type 2 DM were screened for retinopathy between 2001 and 2007.The prevalence of severe diabetic retinopathy was significantly higher in the hypothyroid group compared to the euthyroid group.( 32.8 vs 19.6 p-value = .036)

In our study the number of patients with PDR was only 4 and this number was too less to study an association between thyroid dysfunction and severity of retinopathy.

## LIMITATIONS OF THIS STUDY

-The study population was small.

-The relationship between thyroid dysfunction and severity of retinopathy could not be studied due to the small size of the study population.

-Only hypertension and nephropathy were ruled out among the study population. Factors like dyslipidemia which are associated with both thyroid dysfunction and retinopathy were not ruled out.

-Thyroid function tests did not include free T4 and free T3.

## CONCLUSION

- The prevalence of retinopathy in Type 2 Diabetes patients is 50%.

- The prevalence of thyroid dysfunction among Type 2 Diabetes patients is 23%.

- Sub clinical hypothyroidism is the most common thyroid abnormality among Type 2 diabetics at 21%.

- Prevalence of hypothyroidism in Type 2 DM is 2% and that of hyperthyroidism is 0%.

- Sub-clinical and overt hypo thyroidism are associated with an increased risk of retinopathy.

## RECCOMENDATIONS

- One should have a high index of suspicion regarding the presence of thyroid dysfunction among Type 2 Diabetics.
- Routine screening for Thyroid dysfunction is recommended in all patients with retinopathy.
- Further trials studying the impact of treatment of thyroid dysfunction on the complications of Diabetes need to be carried out.

# PART THREE

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**PROFORMA**

NAME: IP/OP NO:

AGE: DURATION OF DM:

SEX: DATE OF SAMPLE COLLECTION:

OCULAR EXAMINATION:

| RIGHT EYE | | LEFT EYE |
|---|---|---|
| | ANTERIOR SEGMENT | |
| | PUPIL | |
| | LENS | |
| | VISUAL ACUITY | |
| | IOP | |

**THYROID PROFILE**

| PARAMETERS | T3 | T4 | TSH |
|---|---|---|---|
| VALUE | | | |

**RETINOPATHY STATUS**

| | |
|---|---|
| MILD NPDR | |
| MODERATE NPDR | |
| SEVERE NPDR | |
| VERY SEVERE NPDR | |
| EARLY PDR | |
| HIGH RISK PDR | |

IMPRESSION:

# MASTER CHART

| SR NO | NAME | IO/OP NO | AGE | SEX | VISION | IOP | DURATION OF DM |
|---|---|---|---|---|---|---|---|
| RE LE | | | | RE LE | | | |
| 1 | SARASWATI | 635748 | 60 | FEMALE | 6/12,6/12 | 18,18 | 7 YEARS |
| 2 | MALLIGA | 659918 | 60 | FEMALE | 6/9,6/12 | 19,19 | 6 YEARS |
| 3 | NOORJAHAN | 647343 | 56 | FEMALE | 6/9,6/9 | 18,18 | 8 YEARS |
| 4 | MUNIYAMMAL | 647254 | 40 | FEMALE | 6/18,6/24 | 17,17 | 5 YEARS |
| 5 | SHANTI | 647251 | 43 | FEMALE | 6/6,6/6 | 15,16 | 5 YEARS |
| 6 | MUTHURANI | 646480 | 47 | FEMALE | 6/9,6/12 | 20,20 | 8 YEARS |
| 7 | MUTHULAKSHMI | 647262 | 50 | FEMALE | 6/24,6/60 | 19,20 | 7 YEARS |
| 8 | VALLIAMMAL | 648160 | 52 | FEMALE | 3/60,4/60 | 18,18 | 10 YEARS |
| 9 | SERINABEGAM | 650161 | 42 | FEMALE | 6/6,6/6 | 17,18 | 5 YEARS |
| 10 | BACKIYAM | 659745 | 40 | FEMALE | 6/12,6/18 | 18,18 | 6 YEARS |
| 11 | JAYALAKSHMI | 650228 | 56 | FEMALE | 6/24,6/18 | 20,20 | 9 YEARS |
| 12 | TAMILARASI | 650200 | 50 | FEMALE | 6/12,6/12 | 17,17 | 5 YEARS |
| 13 | VEERAYEE | 650242 | 53 | FEMALE | 6/36,6/24 | 18,18 | 8 YEARS |
| 14 | MEENACHI | 630241 | 70 | FEMALE | 6/24,6/60 | 19,20 | 13 YEARS |
| 15 | PANDIYAMMAL | 650571 | 41 | FEMALE | 6/18,6/9 | 17,17 | 7 YEARS |
| 16 | VASANTHI | 650603 | 56 | FEMALE | 6/12,6/9 | 19,18 | 9 YEARS |
| 17 | AARAYEE | 650546 | 44 | FEMALE | 6/9,6/12 | 15,15 | 5 YEARS |
| 18 | PARVATHY | 650616 | 58 | FEMALE | 6/12,6/12 | 18,18 | 10 YEARS |
| 19 | MAHALAKSHMI | 650418 | 61 | FEMALE | 6/18,6/24 | 20,20 | 11 YEARS |
| 20 | SUBBU | 648904 | 40 | FEMALE | 6/12,6/12 | 18,18 | 5 YEARS |
| 21 | RAKKU | 614812 | 80 | FEMALE | 6/18,6/18 | 20,20 | 15 YEARS |
| 22 | OYYAMMAL | 650839 | 58 | FEMALE | 6/6,6/6 | 16,15 | 5 YEARS |
| 23 | PUSHPAM | 650167 | 50 | FEMALE | 6/60,6/36 | 19,20 | 10 YEARS |
| 24 | SELVI | 650294 | 40 | FEMALE | 6/18,6/12 | 15,17 | 6 YEARS |
| 25 | CHINNAPONNU | 650302 | 45 | FEMALE | 6/6,6/6 | 18,16 | 9 YEARS |
| 26 | AMIRTHAM | 84725 | 55 | FEMALE | 6/24,6/9 | 16,17 | 6 YEARS |
| 27 | PICHAYAMMAL | 81706 | 40 | FEMALE | 6/9,6/9 | 17,19 | 7 YEARS |
| 28 | VALARMA | 650961 | 60 | FEMALE | 6/36,6/36 | 19,20 | 9 YEARS |

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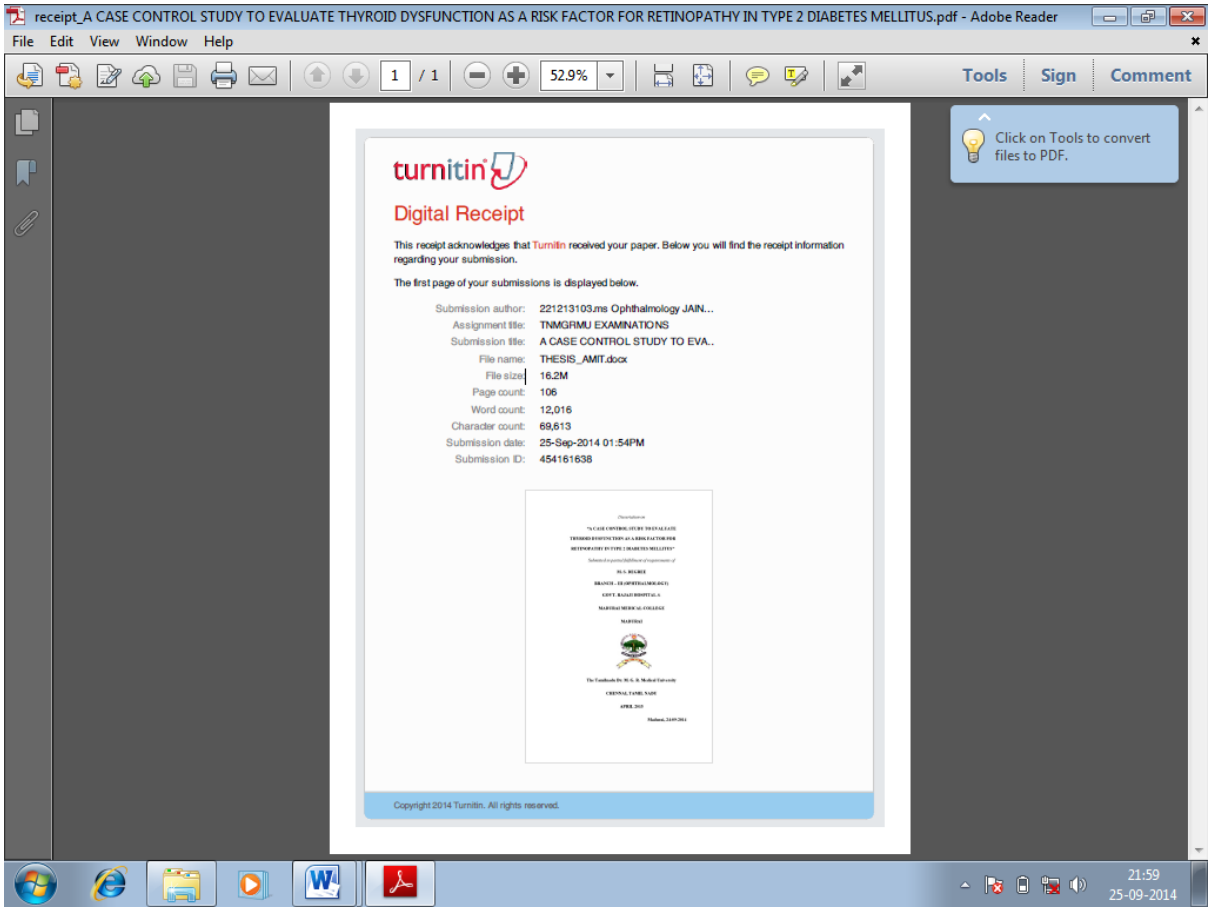
|---|---|---|---|---|---|---|---|
| | THI | | | | | | |
| 29 | ALAGAM MAL | 650990 | 45 | FEMALE | 6/12,6/18 | 15,16 | 8 YEARS |
| 30 | PANDIYA MMAL | 651133 | 54 | FEMALE | 6/18,6/12 | 19,19 | 7 YEARS |
| 31 | VICTORIA MARY | 650960 | 45 | FEMALE | 6/12,6/12 | 18,18 | 6 YEARS |
| 32 | LEELA | 650989 | 70 | FEMALE | 6/60,6/36 | 19,18 | 13 YEARS |
| 33 | VETRISELV I | 651180 | 57 | FEMALE | 6/12,6/18 | 16,16 | 8 YEARS |
| 34 | JOTHIMA NI | 651184 | 47 | FEMALE | 6/12,6/12 | 17,18 | 9 YEARS |
| 35 | KAMALA | 651293 | 67 | FEMALE | 6/18,6/18 | 19,19 | 15 YEARS |
| 36 | ELAMMAL | 651272 | 52 | FEMALE | 6/60,2/60 | 16,17 | 7 YEARS |
| 37 | KAALIAM MAL | 651667 | 57 | FEMALE | 6/12,6/12 | 18,18 | 9 YEARS |
| 38 | GOMATHI | 651731 | 57 | FEMALE | 6/12,6/24 | 14,16 | 6 YEARS |
| 39 | BALAMM AL | 651940 | 63 | FEMALE | 6/12,6/18 | 19,20 | 15 YEARS |
| 40 | KALAISELV I | 651907 | 57 | FEMALE | 6/18,6/18 | 17,18 | 9 YEARS |
| 41 | RAKKAM MAL | 651885 | 48 | FEMALE | 6/12,6/9 | 20,20 | 5 YEARS |
| 42 | LEELA | 652024 | 52 | FEMALE | 6/18,6/12 | 19,19 | 8 YEARS |
| 43 | VALLI | 652031 | 55 | FEMALE | 6/36,6/9 | 18,18 | 10 YEARS |
| 44 | MANJULA | 652052 | 50 | FEMALE | 6/9,6/12 | 18,17 | 6 YEARS |
| 45 | EMILI | 652658 | 65 | FEMALE | 6/60,6/60 | 16,16 | 13 YEARS |
| 46 | ALAGU | 653843 | 58 | FEMALE | 6/24,6/9 | 17,17 | 9 YEARS |
| 47 | VANITHA | 653959 | 47 | FEMALE | 6/6,6/9 | 13,13 | 5 YEARS |
| 48 | ANDICHI | 653912 | 50 | FEMALE | 6/9,6/9 | 15,17 | 10 YEARS |
| 49 | JAYA | 655965 | 58 | FEMALE | 6/18,6/18 | 19,19 | 9 YEARS |
| 50 | VASANTH A | 636691 | 61 | FEMALE | 6/60,6/12 | 14,13 | 7 YEARS |
| 51 | ARUMUG AN | 654175 | 55 | MALE | 6/12,6/18 | 16,15 | 9 YEARS |
| 52 | PALPANDI | 654133 | 70 | MALE | 6/18,6/24 | 17,18 | 12 YEARS |
| 53 | ANBARAS U | 652694 | 48 | MALE | 6/9,6/6 | 12,10 | 5 YEARS |
| 54 | MURGAIY AH | 652693 | 58 | MALE | 6/9,6/9 | 13,12 | 7 YEARS |
| 55 | KANNAN | 653848 | 63 | MALE | 6/12,6/18 | 13,13 | 7 YEARS |
| 56 | VIJAYKUM AR | 611275 | 40 | MALE | 6/9,6/9 | 17,17 | 5 YEARS |
| 57 | RAJA | 653089 | 63 | MALE | 6/6,6/9 | 18,18 | 15 YEARS |
| 58 | SHANTAN U | 653092 | 50 | MALE | 6/12,6/12 | 17,17 | 12 YEARS |
| 59 | JAGANNA THAN | 653115 | 47 | MALE | 6/9,6/24 | 17,17 | 5 YEARS |
| 60 | NAGARAJ AN | 646483 | 48 | MALE | 6/12,6/12 | 15,15 | 8 YEARS |
| 61 | PALRAJ | 647271 | 62 | MALE | 6/9,6/12 | 19,19 | 15 YEARS |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 62 | MOOKAN | 647341 | 53 | MALE | 6/9,6/24 | 16,17 | 9 YEARS |
| 63 | MUTHUSAMY | 647461 | 67 | MALE | 6/12,6/18 | 18,18 | 6 YEARS |
| 64 | MUTHU | 647421 | 65 | MALE | 6/6,6/12 | 17,17 | 10 YEARS |
| 65 | BASKARAN | 647241 | 78 | MALE | 6/12,6/12 | 17,17 | 20 YEARS |
| 66 | CHINNADURAI | 690406 | 58 | MALE | 6/60,6/36 | 19,20 | 8 YEARS |
| 67 | MANOHARAN | 648130 | 45 | MALE | 6/6,6/9 | 14,14 | 7 YEARS |
| 68 | KARUPPASAMY | 648160 | 59 | MALE | 5/60,6/60 | 20,20 | 12 YEARS |
| 69 | SHEIKHDAWOOD | 648187 | 65 | MALE | 6/36,6/9 | 18,17 | 10 YEARS |
| 70 | RAMALAYAI | 648193 | 54 | MALE | 6/12,6/9 | 16,16 | 7 YEARS |
| 71 | RAMAIYA | 648621 | 59 | MALE | 6/24,6/18 | 17,18 | 9 YEARS |
| 72 | SHAKEELAHMED | 648519 | 47 | MALE | 6/12,6/9 | 15,15 | 5 YEARS |
| 73 | MURUGESAN | 648123 | 50 | MALE | 6/6,6/9 | 18,18 | 7 YEARS |
| 74 | SAHULAHMED | 649372 | 37 | MALE | 6/6,6/6 | 13,13 | 5 YEARS |
| 75 | HARIKRISHNAN | 649351 | 66 | MALE | 3/60,1/60 | 20,20 | 16 YEARS |
| 76 | DEVENDRAN | 649338 | 56 | MALE | 6/36,6/9 | 18,17 | 8 YEARS |
| 77 | MURUGAN | 678864 | 60 | MALE | 6/24,6/24 | 17,17 | 9 YEARS |
| 78 | VEERASAMY | 649402 | 58 | MALE | 6/9,6/9 | 16,16 | 12 YEARS |
| 79 | MAHALINGAM | 649342 | 54 | MALE | 6/36,6/60 | 18,18 | 9 YEARS |
| 80 | SELVARAJAN | 649642 | 46 | MALE | 6/9,6/12 | 15,15 | 7 YEARS |
| 81 | VAHAB | 649671 | 50 | MALE | 6/9,6/12 | 16,16 | 14 YEARS |
| 82 | NARSEEMA | 650159 | 45 | MALE | 6/9,6/9 | 13,13 | 7 YEARS |
| 83 | GANESAN | 650227 | 65 | MALE | 6/60,6/12 | 15,15 | 10 YEARS |
| 84 | RAJASEKAR | 650213 | 58 | MALE | 6/18,6/12 | 17,18 | 11 YEARS |
| 85 | ABDULKAREEM | 650249 | 66 | MALE | 6/12,6/9 | 19,20 | 8 YEARS |
| 86 | RAJA | 650644 | 48 | MALE | 6/12,6/9 | 14,14 | 5 YEARS |
| 87 | SUBAHAN | 650707 | 58 | MALE | 6/24,6/18 | 15,16 | 9 YEARS |
| 88 | PARAMASIVAM | 650852 | 42 | MALE | 6/12,6/12 | 17,17 | 6 YEARS |
| 89 | MURUGAN | 650895 | 52 | MALE | 6/9,6/60 | 18,18 | 5 YEARS |
| 90 | GOVINDHRAJ | 650273 | 51 | MALE | 6/12,6/18 | 17,18 | 7 YEARS |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 91 | KARTHIK | 650305 | 45 | MALE | 6/12,6/9 | 19,17 | 5 YEARS |
| 92 | MUTHU | 650335 | 49 | MALE | 6/6,6/6 | 13,13 | 5 YEARS |
| 93 | DEVARAJ | 650297 | 54 | MALE | 4/60,6/60 | 18,18 | 9 YEARS |
| 94 | JAYARAM | 650367 | 51 | MALE | 6/12,6/12 | 17,17 | 7 YEARS |
| 95 | SELVAM | 650311 | 60 | MALE | 6/12,6/18 | 15,15 | 8 YEARS |
| 96 | RUSHTAM | 650299 | 57 | MALE | 6/60,6/36 | 19,19 | 5 YEARS |
| 97 | PERIYAKARUPAN | 650310 | 65 | MALE | 6/12,6/12 | 14,14 | 15 YEARS |
| 98 | MAHENDRA | 650300 | 55 | MALE | 6/9,6/9 | 17,17 | 8 YEARS |
| 99 | CHINNARAMAN | 650992 | 60 | MALE | 6/12,6/12 | 17,17 | 10 YEARS |
| 100 | PITCHAI | 651141 | 69 | MALE | 6/9,6/9 | 17,17 | 20 YEARS |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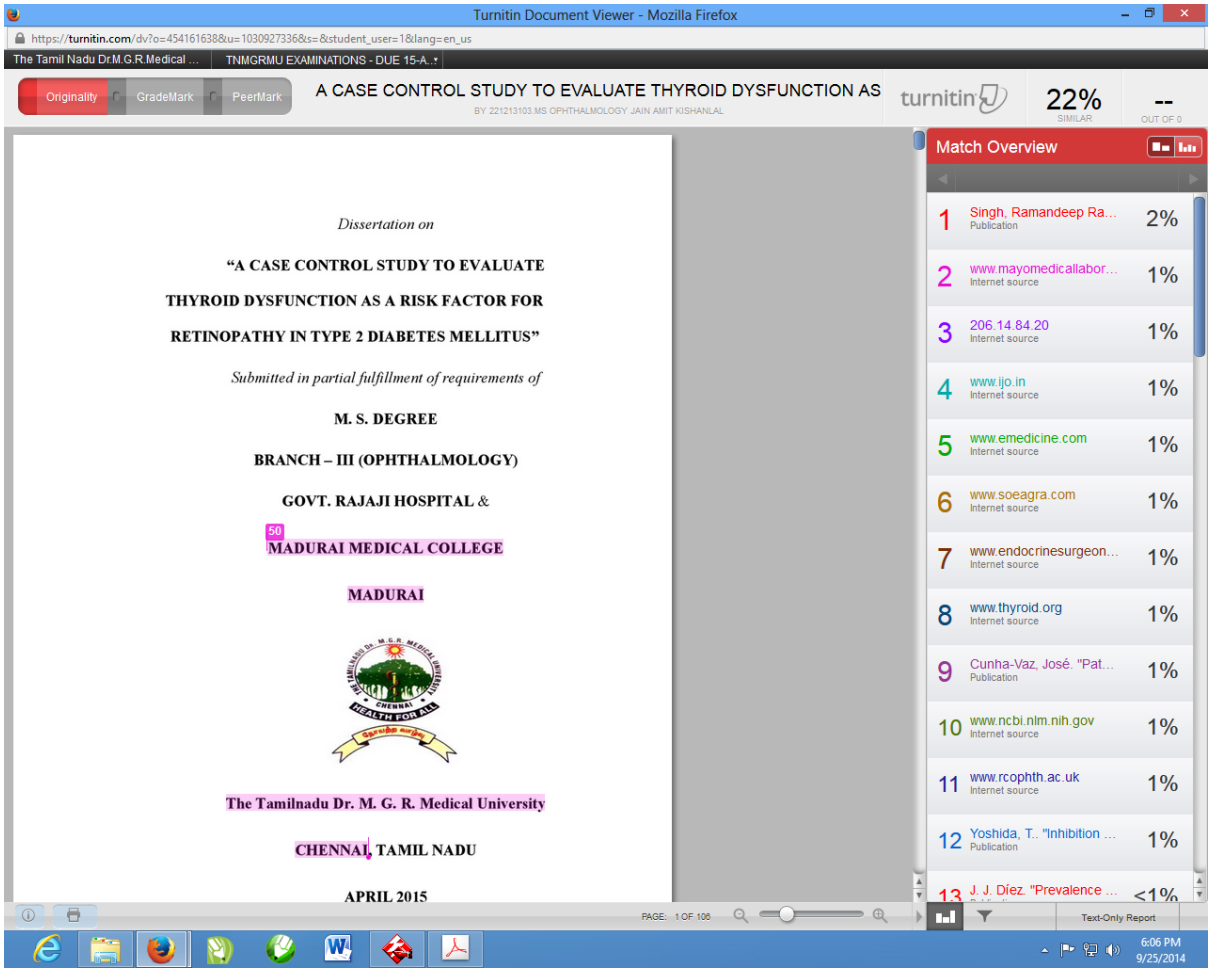
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Submitted in partial fulfillment of requirements of
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GOVT. RAJAJI HOSPITAL &
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